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An Interoperable Clinical Cardiology Electronic Health Record System – a standards based approach for Clinical Practice and Research with Data Reuse

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Contents

Abstract

Currently in hospitals, several information systems manage, very often autonomously, the patient's personal, clinical and diagnostic data. This originates a clinical information management system consisting of a myriad of independent subsystems which, although efficient in their specific purpose, make the integration of the whole system very difficult and limit the use of clinical data, especially as regards the reuse of these data for research purposes. Mainly for these reasons, the management of the Genoese ASL3 decided to commission the University of Genoa to set up a medical record system that could be easily integrated with the rest of the information system already present, but which offered solid interoperability features, and which could support the research skills of hospital health workers. My PhD work aimed to develop an electronic health record system for a cardiology ward, obtaining a prototype which is functional and usable in a hospital ward. The choice of cardiology was due to the wide availability of the staff of the cardiology department to support me in the development and in the test phase. The resulting medical record system has been designed "ab initio" to be fully integrated into the hospital information system and to exchange data with the regional health information infrastructure. In order to achieve interoperability the system is based on the Health Level Seven standards for exchanging information between medical information systems. These standards are widely deployed and allow for the exchange of information in several functional domains. Specific decision support sections for particular aspects of the clinical life were also included. The data collected by this system were the basis for examples of secondary use for the development of two models based on machine learning algorithms. The first model allows to predict mortality in patients with heart failure within 6 months from their admission, and the second is focused on the discrimination between heart failure versus chronic ischemic heart disease in the elderly population, which is the widest population section served by the cardiological ward.

List of abbreviations

ACE	Angiotensin-Converting Enzyme
ADT	Admit, Discharge and Transfer
AI	Artificial Intelligence
AIC	Autorizzazione all'Immissione in Commercio
ALT	Alanine Aminotransferase
AO	Azienda Ospedaliera
API	Application Program Interface
ASL	Azienda Sanitaria Locale
AST	Aspartate Aminoransferase
AUPRC	Area under Precision Recall curve
AUROC	The Area under the receiver operating characteristic
CEHRS	Cardiology EHR System
CDA	Clinical Document Architecture
CDS	Clinical Decision Support
CDSS	Clinical Decision Support System
CIHD	Chronic Ischemia Disease
CRP	C-reactive protein
CTS2	Common Terminology Services Release 2
DSS	Decision Support Systems
DSTU	Draft Standard for Trial Use
EF	Ejection Fraction
EHR	Electronic Health Record
EMR	Eletronic Medical Record
FC	Fiscal Code
FHIR	Fast Healthcare Interoperability Resource
FPR	False Positive Rate
FSE	Fasicolo Sanitario Elettronico
GEM	Guideline Elements Model

GFR	Glomerular Filtration Rate
GLIF	Guideline Interchange Format
Hb	Hemoglobin
HDLET	Hospital Discharge Letter
HDL	High-density lipoprotein
hs-cTnT –I	High -sensitive Cardiac Troponin I
HF	Heart Failure
HII	Health Information Infastructure
HIMSS	Healthcare Information and Management Systems Society
HIS	Hospital Information System
HL7	Health Level 7
HL7 V2	Health Level 7 Version 2
HL7 V3	Health Level 7 Version 3
HSSP	Healthcare Services Specification Project
ICD	International Classification of Diseases
ISO	Identification Service
ISO	International Organization for Standardization
IT	Information Technology
IXS	Cross-Reference Service Release 1
JSON	JavaScript Object Notation
KM	Knowledge Module
LDL	Low-density lipoprotein
LOINC	Logical Observation Identifiers Names and Codes
ML	Machine Learning
MLM	Medical Logic Modules
OID	Object Identifier
OMG	Object Management Group
PACS	Picture archiving and communication system
PID	Patient Identification
PR	Precision-Recall

PSM	Platform Specific Model
RHII	Regional Health Information Infrastructure
RIM	Reference Information Model
RIS	Radiology Information System
RLUS	Retrieve, Locate and Update Services Release 1
ROC	Receiver Operating Characteristic
RWD	Real Word Data
SFM	Service Functional Model
SNOMED	Systemized Nomenclature of Medicine Clinical Terms
SOA	Service Oriented Architecture
SOAP	Simple Object Access Protocol
SQL	Structured Query Language
STM	Service Technical Model
SVM	Support Vector Machine
THR	Classification Thresholds
TPR	True Positive Rate
UML	Unified Modeling Language
VB	Visual Basic
VMR	Virtuale Medical Record
WCF	Windows Communication Foundation
WSDL	Web Service Description Language
XML	eXtensible Markup Language
XPDL	XML Process Definition Language
XSD	eXtensible Markup Language Schema Definition

1 Introduction

1.1 BACKGROUND

Healthcare is currently changing, focusing on prevention and early diagnosis, primary care, home care and continuity of care. This requires the availability of a wide range of knowledge and tools to improve various aspects of the professional activity of doctors; among these, they also contribute to the achievement of an optimal diagnosis and therapeutic decisions. One such tool is the electronic health record (EHR), which represents an essential technology for healthcare[1].

An EHR is an electronic version of a patient's paper medical record that contains the patient's entire episode of hospitalization in the care institution. For the operator involved in the treatment of any patient, it is often important to know the data recorded by other health professionals who provide that patient because these data provide information on the patient's health status, current and previous medications, allergies, diagnoses from other episodes. treatment, exam results, etc. EHR and digital patient data have gained the vital role in both health care and continuity of care.

The Health Information Management Systems Society (HIMSS) defines EHR as:

a longitudinal electronic record of patient health information generated by one or more encounters in any care delivery setting. Included in this information are patient demographics, progress notes, problems, medications, vital signs, past medical history, immunizations, laboratory data, and radiology reports. The EHR automates and streamlines the clinician's workflow. The EHR has the ability to generate a complete record of a clinical patient encounter, as well as supporting other care-related activities directly or indirectly via interface, including evidence-based decision support, quality management, and outcome's reporting. (p. 1)

In antiquity written case history reports were developed for didactic purposes in Egypt and in Greece. A forerunner of modern medical records first appeared in Paris and Berlin by the early 19th century. Developments of the clinical record in Western countries was carried out in the 19th century in teaching hospitals, but clinical medical records for direct patient care were only developed in the 20th century [2].

The adoption of electronic medical records among doctors and healthcare professionals has been slow and the debate on medical records in the scientific world is still open and has been going on for many years.

A review of the literature in 2016 [5] identifies three moments in the evolution of the EHR:

- Beginning of the real expansion of the portfolio (90s)
- Beginning of maturity of the EHR systems (with a fixed time point in 2015)

- The vision for the future or what the Medical Record will be like (from 2015 onwards)

Evans highlighted that at the beginning of the 90s the community of objects pertaining to health information systems was enriched with various specializations and therefore the need aroused for a communication between them and with the clinical record which was and remains the center of information systems. So, at the beginning of the 90s the debate for the use of standards deepened.

The rise in applications and the need for EHRs to interface with them highlighted that a wide use of standards was needed. The standards were only partially used and the need emerged for support modules for operators in order to achieve a more effective use of the available tools.

In spite of the partial adoption of standards in 2015 it was felt that the expectations reported in the 90s were still present. In [5] the authors remark the following problems:

- Lack of standards
- Unavailability of interoperability services
- Inability of the physician to fully describe the patient's medical history within the EHRs
- Inflexible, unintuitive, expensive, difficult to maintain and poorly interoperable EHRs
- Differences in semantics and used dictionaries
- Lack of input and testing from doctors in application design and development

Current EHRs do not meet the needs of today’s distributed systems and of the rapidly changing healthcare environment. It was predicted [5] that in the future clinicians will have more control over the personalization of EHR , resulting in greater adaptation to their needs and preferences, such as intuitive graphical user interfaces based on internationally accepted standards, integrated health information exchange capabilities with pluggable application programming interfaces and open services, patient specific, linkable, interchangeable and API-based clinical decision support (CDS) modules, independent of EHR versions and updates.

1.2 The current context of the EHR

The use of information and communication technologies for health is being increasingly adopted globally. In 2005, the World Health Assembly invited member states to consider setting up long term strategic plans for the development and implementation of e-Health services and to develop suitable infrastructures. Since then, more than 120 member states have developed strategies and polices in this respect [6] .

In 2013, a resolution on e-Health standardization and interoperability was adopted, which invited member states to develop policies and legislative mechanisms for national e-Health strategies, and in

2020, the global strategy on digital health 2020–2025 was endorsed, which set up a framework to advance digital health globally and within countries [6].

While traditional patient records have been illness focused, healthcare now focuses on the continuum of health and healthcare from wellness to illness and recovery, and EHRs will increasingly carry a greater portion of a person health-related information, including images, electrophysiologic monitoring and genomic information [8], [9]. EHRs have the advantage of availability of information, entry controls and capability, increase in data quality by validity checks and conditional data entry, depending on the value of the other data [9]. Relevant benefits of care quality have been found, and, in addition to clinical care outcomes, EHR systems have been found to affect the costs and efficiency of healthcare systems [10] .

The adoption of EHR systems automates data management, simplifies the clinician's workflow and supports care related activities, integrating data for different purposes, such as treatment effectiveness analysis, adverse condition reporting, research and administrative aspects. The foreseeable widespread adoption of EHRs can improve quality, safety and efficiency in healthcare, even though several challenges still need to be overcome. Moreover, EHR systems, which have been increasingly implemented everywhere, represent a vast data resource for biomedical research and clinical care [11], [12]. The secondary use of EHRs has been carried out for many areas, such as in cardiology [13], [14], oncology [15], [16], ophthalmology [17], [18], rheumatology [19], [20], and others.

Enhanced standardization can bring about significant improvements in healthcare [22][21].

The standardization of medical information is receiving increasing attention, due to the need of sharing, exchanging, storying and querying of patient data among hospitals, health departments, health centres, physician's offices, laboratories and the patients. In order to support the development of interoperable and reliable medical systems, several medical standards are used, mainly developed by HL7, such as Clinical Document Architecture (CDA) [23][22], Fast Healthcare Interoperability Resources (FHIR) [24][23] and others.

The first significantly successful HL7 standard was version 2, which, even though introduced in 1987 is still widely used in clinical implementation. However, its great success and excessive malleability has brought about a myriad of bilateral agreements among companies in order to solve specific problems using the widely available customizations of version 2. In 2006 it seemed obvious that this huge amount of customizations was not controllable, therefore HL7 decided to restart defining a standard strictly deriving from RIM, and produced version 3. The strictly deductive aspect of version 3 brought about very robust and successful structures like CDA, however, for an extensive use in all health information systems is was found to be too cumbersome and failed to establish itself in the vendors market. Vendors mostly continued to use version 2. In 2001 HL7 decided to start yet again

with the definition of a standard, with the objective of setting up an easy to use, standard that could use a wide on line documental library. This standard should also be mainly based on RIM. Another objective of this version is to be easily interfaceable with mobile tools. This led to FHIR standard definition.

The basic building blocks of FHIR are generic definitions of common healthcare concepts (such as patient, practitioner, observation etc.), which can be ex-changed in eXtensible Markup Language (XML) or JavaScript Object Notation (JSON) format and are intended to cover typical use cases [25]. Since its introduction, FHIR is being increasingly adopted and is regarded as an emerging standard for health data ex-change in many domains, including EHRs.

Currently in hospitals there are several separate information systems that manage, very often autonomously, the patient's personal, clinical and diagnostic data. The main ones are the management of booking centre, the hospitalization management, the picture archiving and communication system (PACS) and the radiological information system (RIS). Sharing information among these systems and interoperability are needed.

There are more and more studies in literature showing that interoperability is important to fully exploit the potential of digitization in healthcare and medicine [26].

Although the importance of interoperable health IT systems is increasingly recognized, awareness of this topic is still relatively low among healthcare professionals, especially with respect to topics such as artificial intelligence (AI), big data or mobile technologies, which are generally considered to be the main innovation in digital healthcare. As a result, progress in health interoperability is slow.

Today's healthcare IT systems operate with a wide variety of data formats, custom specifications, and ambiguous semantics. This situation is aggravated by the tendency to store increasing amounts of unstructured data in non-relational databases

Furthermore, running algorithms on unstructured and non-standardized data can introduce errors that skew the results of the analysis [26]

While this unstructured data is arguably better than no data and modern algorithms can extract some useful information even from unstructured data it is difficult to process. As a result, time-consuming data cleanup and preprocessing procedures are usually required prior to analysis.

The main aim of my PhD project is to design, develop and test an electronic health record system that has been specifically devoted to the work in a cardiology ward. The limitation to one discipline is due to the limited time of the period of study and to the need to have a prototype that is really functional and usable in a real hospital ward in three years.

In the first and second year of this PhD project an EHR system for a cardiology was developed ward “ab initio”, to be fully integrated into the Hospital Information System (HIS) and to exchange data with the Regional Health Information Infrastructure. In order to adequately support interoperability, extensive use was made of the best-known standards of medical informatics, especially those proposed by HL7 (V2, CDA and FHIR). Specific decision support sections for specific aspects were also included.

The main objective of the third year was to demonstrate the feasibility of a machine learning (ML) support tool starting from well-structured and interoperable real data got through the routine use of a Cardiology EHR System (CEHRS). Specifically, I focused on two aspects:

- The development and validation of a ML based pipeline that uses EHR structured data to predict mortality among patients with Heart Failure (HF) within 6 months from their hospitalization.

-The development and validation of a predictivity tool to discriminate HF against Chronic Ischemic Hearth Disease (CIHD) in crucial moments when patients are hospitalized at the cardiac or emergency care unit with serious symptoms. This model can be used as a direct aid to clinical decision making and likely help in reducing the time in relation to establish a diagnosis.

The development of the CEHRS started in 2018 and was based on agile development methods since during all stages users could test the developed products on an almost basis, achieving a very close user-developer interaction.

This CEHRS has been adopted and is currently used in two hospitals (Villa Scassi and Padre Antero Micone) in Genova; these hospitals are part of the Liguria Region Healthcare System.

1.3 Objectives

The Liguria region has financed this PhD to design, develop and test an EHR system designed "ab initio" to integrate fully into the HIS and to exchange data with the regional health information infrastructure (RHII) which related with the national initiative “Fasicolo Sanitario Elettronico” (FSE).

One of the main objectives of the project was to design, manufacture, implement and test a new modular EHRS for use in the cardiology wards of local hospitals. The main objective was to replace the paper-based system, which had been previously used for a long time in the two hospitals with an EHRS, while retaining staff reliance.

The interoperability features of this EHRS allow collecting high-quality structured data and its re-use in scientific research. Therefore, we analyzed the applicability of an AI pipeline starting directly from

the Real Word Data (RWD) collected by our system. The main challenge is to demonstrate that good results can be achieved starting from interoperable and well-structured RWD.
In order to demonstrate the effectiveness of the developed EHRS as a tool to support clinical research of the medical personnel I tried to use the data collected from the EHRS during the routine use period of by applying some of the most used artificial intelligence models. In this way I was able to develop two predictive / discriminatory models which are described below.

In the first model, I faced the problem of mortality due to HF. According to the Ministry of Health, in Italy, HF is the leading cause of hospitalization in people over 65s, thus, it is considered an urgent public health problem. About 600,000 people suffer from HF and its incidence is estimated to double for every decade of age (after the age of 65 it reaches about 10%) [27]Therefore, it is important to identify patients linked to a higher risk of mortality due to HF and determine the impact of pharmacological therapies on their outcomes [28]. So, the aim of our work was to develop and validate a ML based pipeline that uses structured EHR data to predict mortality among patients with HF within 6 months from their hospitalization.
In the second model I tried to develop a tool to support discrimination between HF and CIHD. It aims to decrease the number of misdiagnosed cases of heart failure against chronic-ischemic heart disease according to the prediction of specific blood analysis parameters applying ML techniques.

2 Materials and Methods

This section describes the tools that I have used to achieve the objectives described in the previous chapter. This section is divided into two parts, one relating to the development tools of the EHRS (with special reference to interoperability) and one relating to the ML tools that were the basis of the two models I have developed.

2.1. EHRS development tools

The chosen architecture of the EHRS is based on central/federated databases (one per hospital) and an interactive web-based platform. The database has been developed using Microsoft SQL Server as the data base management system, implemented with Visual Studio, through.NET framework and deployed on the an extensible web server software created by Microsoft called at present Internet Information Services.

One of the main requirements for the whole project is to be integrated with both the HIS and with the RHII.

A corporate/regional/national health information infrastructure (HII) is intended to provide timely health information and to facilitate communication between people involved in the health sector. Healthcare professionals and public health professionals are the primary users of HII, and applications that meet their needs are important components of the infrastructure. To ensure interoperability, HII uses standards, and integrates systems, applications and technologies that support personalized health services through the effective integration of information from information sources on the web.

Healthcare in Italy is directly managed by regions and the National/Governmental level only has a weak coordination role. Each Italian region developed its own HII, but they agreed on an institutional centred approach for its architecture, such as the one presented in Figure 2.1.

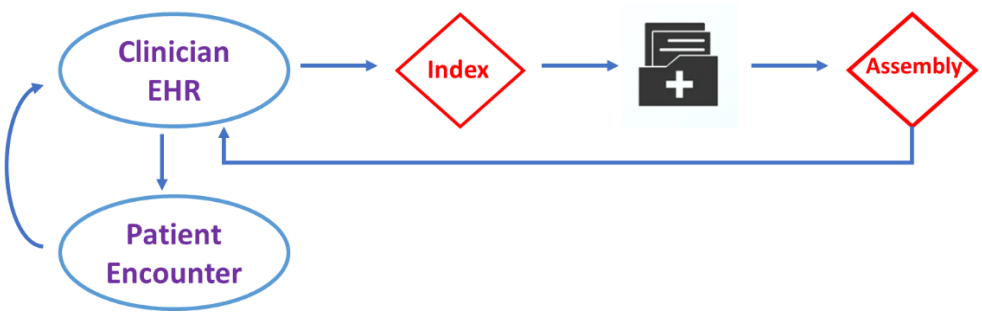

Figure 2.1. A scheme of the HII, typically used in Italian regions.

As the records are not centrally stored, at least one central index is needed, from which the information for a particular patient can be extracted. When the patient data are requested, the index is used to query the repository where the stored information is located. The answers to these questions are then assembled (in real time) to produce the complete patient record data. After examining the patient, the new data are entered into the physician's EHR system.

The architecture that has been developed integrates a routinely used cardiological EHR system into the RHII system present in the Liguria region. According to the rules by the Italian Government [29], all documents of the FSE and of the Liguria RHII should be given as HL7 CDAs and messages should be sent as HL7-Version 2 (V2) and/or HL7 FHIR. Therefore, all external interfaces of the CEHRS have been designed and developed according to a service oriented approach (SOA) based on a Healthcare Services Specification Project (HSSP) that uses CDA, V2 and FHIR as the semantic signifier [8][12]. In order to obtain a fully interoperable system at all levels defined by the Clinical Data Interchange Standards Consortium, the CEHRS can be interfaced also with a terminology service [28][30].

2.2 Interoperability

The term interoperability expresses the concept, which today is increasingly widespread in many sectors, to allow, through unifying procedures, interchange and interaction in information technology (IT), telecommunications, transport and security systems.

Interoperability, in the IT field, is defined as the capacity of a system or a computer product to cooperate and exchange information or services with others systems or products in a more or less complete and error-free manner, with reliability and with resource optimization[31].

Its goal is to facilitate the interaction between different systems, as well as the exchange and the reuse of information even between non-homogeneous information systems (both for software and hardware).

The term interoperability is used in the technological field to indicate a high degree synergy of different systems in order to offer new services or features. It is directly linked to the tendency to converge a wide range of technologies on certain advanced technologies services.

The Institute of Electrical and Electronics Engineers defines interoperability as: “the ability of two or more systems or components to collaborate, exchanging information and using such information effectively, without particular difficulties” [32].

Three aspects allow interoperability to be distributed (Figure 2.2) [32]:

1. Technical interoperability;

2. Semantic Interoperability;

3. Process Interoperability.

Technical interoperability is the best known aspect, and relates to telecommunications, to software and to the continuous evolution of computing systems. The domestic use of IT puts us every day in the face of the need for interoperability between the different systems we have. HL7 defines technical interoperability as "the ability to transporting a datum from a system A to a system B" [32].

Semantic interoperability relates to the rational way in which system complexes, private and public, national and supranational, are able to cooperate synergistically.

Therefore, according to HL7, interoperability can be seen as "the capacity that ensures that both systems interpret data in the same way ” [32].

Process interoperability is "the ability that allows business processes systems A and B to work together requiring minimal interaction with the user " [32].

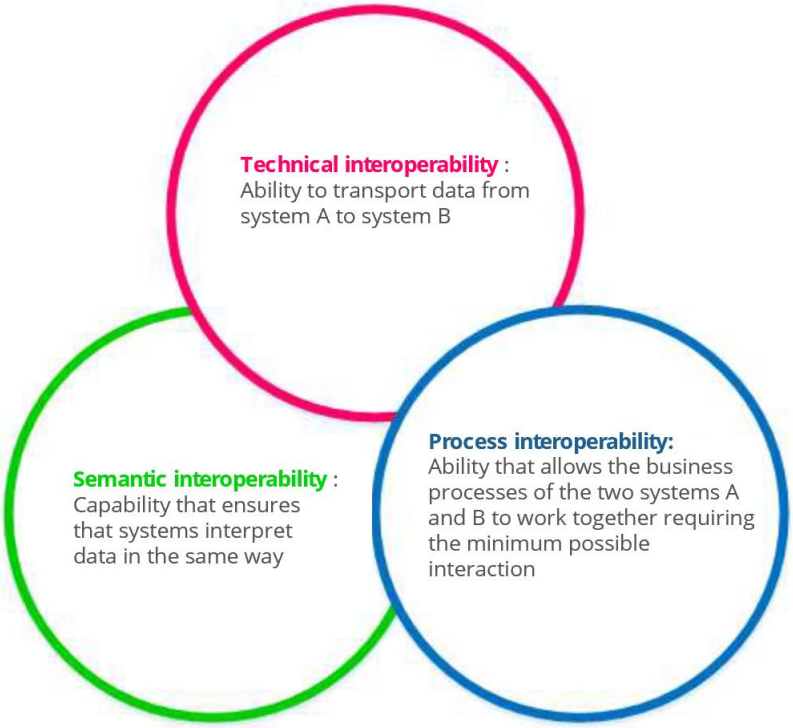

Figure 2.2: Interoperability levels according to the HL7 definition

As for the world of healthcare, interoperability between information systems hospital management, electro-medical and diagnostic equipment is one of the fundamental roads to go through to provide better continuity of care to patients. In this sector, the integration between systems is a problem due to the size and specificity of this sector, which is very complex and articulated and devoid of organic development.

2.3 HL7

HL7 International is a non-profit organization founded in 1987, accredited as Standards Development Organization (SDO) by American National Standard Institute (ANSI), with the aim of providing a complete picture and related standards for the exchange, integration, sharing and recovery of electronic health information that supports clinical practice and management for the delivery and evaluation of health services.

HL7 is now supported by over 1,600 members from over 50 countries, including:

- over 500 companies
- members representing health professionals

- government stakeholders
- taxpayers
- pharmaceutical companies
- sellers / suppliers
- consulting companies

HL7 is the most popular standard for message communication in the Information and communication technologies (ICT) sector in healthcare.

A standard, in IT, can be defined as: "a unofficial or official set of standards, recommendations or specifications, purely conventional, pre-established by an authority and recognized as such with the purpose of represent a reference base or coded paradigm for the realization of mutually compatible and interoperable technologies, which are hardware components, network software or infrastructure" (ISO / IEC Guide 2: 2004).

The very acronym of the association, HL7, serves to emphasize that all proposed solutions work at the 7th level of the ISO / OSI hierarchy, that is the level application, which is the highest level (Figure 2.3).

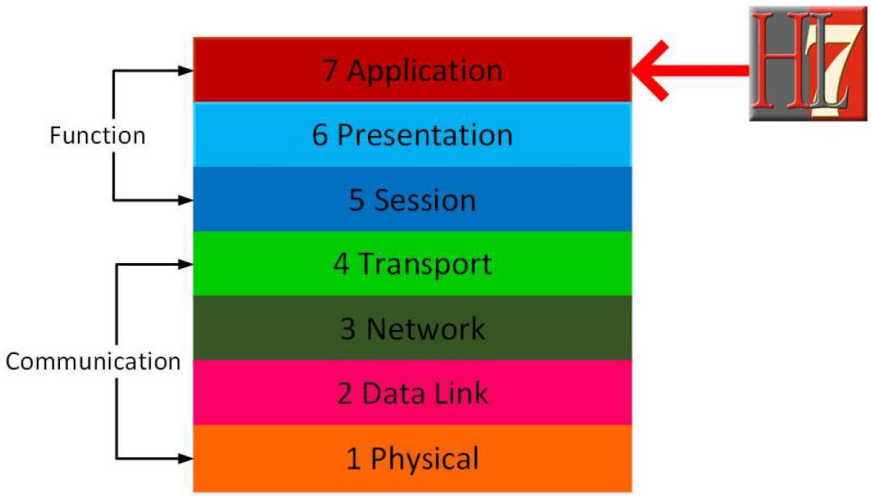

Figure 2.3: ISO-OSI model levels

The seventh level supports functions such as:

• security check

• identification of the participants

• checking availability

• negotiation of exchange mechanisms

• structure for data exchange.

The HL7 standard is developed and updated by a committee of users and manufacturers with the common goal of simplifying the interfaces between applications from different manufacturers, often antagonists, and standardize the format and protocol used in the exchange of some critical data sets. It basically defines the messages to be exchanged, the methods of synchronization of the exchanges and the specifications of the error messages.

Compatibility with the standard does not necessarily imply compatibility between systems that have adopted it. In fact, as relates to the levels below level 7, the HL7 standard assumes that the communication protocols are compatible, without imposing constraint details. Furthermore, it does not intervene on the way in which the information is presented or managed and can therefore be easily integrated into different types of software solutions.

Relating the location and sharing of data, HL7 does not impose particular conditions to the overall system architecture, and can be adopted in very heterogeneous environments, with centralized or distributed architectures between individual departmental systems.

The specifications are strongly oriented to ensure ample flexibility, which takes into account the particular needs of each environment and each user, with the aim of a long term, to allow for the elimination or strong reduction of proprietary interfaces and associated programming and maintenance costs.

The most used specifications are those for the exchange of standardized messages, and currently available versions of HL7 are HL7 v2, HL7 v3 and FHIR.

2.3.1 HL7 V2

The first standard version 2 was created in 1989 and has been constantly revised and updated since then. This version deals specifically with message standardization.

The first V2 versions were rather inaccurate and lacking in formal specifications but subsequently, with the growth of the adoption of the standard, more and more specific version where produced to cover an increasing number of areas, while maintaining compatibility with previous versions. HL7 V2 consists of text messages formatted using certain characters. HL7 V3 is less used with respect V2 version for the following reasons:

• it is more complex

• it is not backward compatible with version V2

• it have fewer options than version V2

• it has higher cost since V3 is not compatible with previous versions and, since most systems still use the V2 version, it is from time to time necessary to convert a version interface V2 existing in version 3, which in addition to being time consuming, can be hard.

An HL7 V2 message is meant to pass information about a certain event from one system to another. There are various types of messages identified by a three-letter code; the event that triggers the start of a communication is called a “trigger” event.

The HL7 V2 message is a textual content, consisting of a header and an ordered sequence of segments. Each segment has a code that defines the content (for example PID stands for Patient Identification) and is composed of fields which have well-defined positions. For example for PID, information such as surname, name, tax code and date of birth of patient can be found. These are delimited with the "|" character and, within them, the same field can also be divided into several sub-fields, in turn delimited by the "^" character. For example for the PID segment, the address is contained between two "|" and the sub fields can be found, street, house number, post code, city, province.

These features of the HL7 message can be seen in Figure 2.4. Some of the available types are shown in the following:

• ADT - Admission, Discharge and Transfer: transmission of data that concern admissions (Admission), discharges (Discharge) and transfers (Transfer)

• ORM - Order Message: transmission of information on an order

• ORU - Observation Result: messages regarding the results of observations, usually it is in response to an order

• ACK - Acknowledge: used to signal the correct reception of the message

```
MSH|^~\&|Rapidcomm|Hospital|HIS|Hospital|201506051656||ORU^R32|
0C0634M000Z000010404|P|2.3|||AL|AL|
PID|1||MRN^^^||LNAME^FNAME^MNAME^^^||DOB|SEX|||ADDR^^CITY^STATE^PCODE^
^^||PHONE|||||ACCOUNT^^^|SSN|||||||
ORC|NW|ACCESSION|^|^|IP||001^^^201506061014^201506061014^S^^^^||201506
061014|||OPHYID^OPHYNAME ^^^^^^|||||||
OBR|1|PORDER|FORDER|Urinalysis||||||S^^^^^^^|O|||||
OPHYID^OPHYNAME^^^^^^||||||||||001^^^201506061014^201506061014^
S^^^^| ||||||||201506061014|
OBX|1|ST|ALB||10|mgL|||||F|||20150601112058||ROID^ROLNAME^ROFNAME||^^4
001^CLINITEK Status|20150601112058|
OBX|2|ST|BIL||Small||||||F|
OBX|3|ST|GLU||100|mg/dL|||||F|
```

Figure 2.4: Example of HL7 V2 message

Each message type can be associated with different trigger events: the operations to transfer and register a patient are, for example, two different trigger events in the ADT message. An example is shown in Figure 2.5.

```
MSH|^~\&|HIS|Hospital|Rapidcomm|Hospital|200506051656||ADT^A03|
17-1-35:CC1JGE|P|2.3|||AL|NE|
EVN|A03|||||200508300930|
PID|1||MRN^^^||LNAME^FNAME^MNAME^^^||DOB|M|||ADDR^^CITY^STATE^PCODE^^^
||PHONE|||||ACCOUNT^^^|SSN||||||||
PV1|1|I|31^3107^1^^|E|||APHYID^APHYNAME^^^^^^|RPHYID^RPHYNAME^^^^^^|||
|||||||
```

Figure 2.5: Example of ADT message

An HL7 message has three types of segments: mandatory, that is always present within the same message, optional, which can be omitted, and repeatable, wich can be present several times in a message. Moreover, each segment of mandatory and optional fields. The first must be present in the message for correct operation, while optional fields can be used if desired. Each HL7 segment end with a carriage return which, being an ASCII 13 code (character not printable), it will not be shown when viewing the message. Some segments are shown below.

• MSH - Message Header: each message always begins with this segment, which defines the intent, origin, destination of a message and contains the Message Control ID (MCI), which is used to confirm receipt of an HL7 message

• PID - Patient Identification: contains patient specific information

• PV1 - Patient Visit Segment: is used to communicate specific information for the patient visit. Messages can contain multiple PV1 segments to communicate information on multiple patient visits.

• OBX- Observation/Result is used to carry the key information of a clinical observation. This segment can be used multiple times in the same message.

Since HL7 is the format used for the exchange of messages in this project, its structure is shown by an example of the ADT. This message has several mandatory segments which are: MSH, EVN, PID, PV1 suitably inserted in Figure 2.5; in this case, not there are optional segments. The trigger event of this ADT message is A03, as shown in MSH field 9.2, i.e. segment MSH, field 9, below field 2. The A03 event of an ADT message signals the end of the stay of a patient in a healthcare facility.

2.3.1.1 The exchange of messages

HL7 V2 messages are typically sent over a connection between two systems. Each system has a role: one acts as a client and the other as a server. Often the one sending the data is the client, but it is not always the case. There are two ways in which messages are exchanged:

• Unsolicited: defines an interface that will send HL7 results without that is required, requiring only a Transmission Control Protocol (TCP) connection to be established with the receiving system. The receiving system responds with a message ACK type.

• Solicited: defines an interface that will send a QRL HL7, message of query, which requests data from a source system, first of all establishing a TCP connection with it.

Moreover, it is possible to identify two types of communication which are:

• Unidirectional: communication occurs in one direction only. It is considered unidirectional even if an ACK is returned by a destination, when an HL7 message is recognized

• Bidirectional: the roles of the sender and the receiver are continuously exchanging, establishing an additional communication flow directions. The client opens a TCP / IP socket with the server and, this connection, comes used exclusively for communication between these two systems.

Much of the HL7 messaging is set up by the Minimal Lower Layer Protocol, also known as Lower Layer Protocol. For transmission, header and tail characters are added to the message for identifing the beginning and the end, because TCP / IP is a continuous stream of bytes. A once the connection is established, the sending system can deliver an HL7 message.

2.3.2 HL7 V3

HL7 V3 is an object-oriented standard, the content of which is based on the concept of information model, that is a specific structure of the information contained within a particular domain of interest.

HL7 V3, just like V2.x, is a standard for exchanging messages between information systems that implement health care applications, but V3 aims to improve methods and results, and to overcome the limits detected over time by the previous version.

Since 1996, HL7 has tried to remedy the conceptual and structural problems of V2 through the study of a new development model, which could lead to the creation of the new V3 standard, wich is more structured. The purpose was obtain more rigorous and defined standard, which could reduce the uncertainties of its implementation and consequently its costs.

HL7 V2 is currently the most implemented standard for health information worldwide, but compatibility with this standard does not imply direct interoperability between health systems. This stems from the fact that V2 messages don't have a well termed basic information model, the definitions for many data fields are quite vague and there are a multitude of optional data fields.

These options offer great flexibility, but require mandatory agreements between health systems to achieve interoperability. One of the strengths of V3 messaging is precisely the ability to allow two information systems to exchange refined data without research and negotiation that V2 requires to deal with.

In addition, the HL7 V3 takes into account any evolutions of the future IT scenario, preventing as far as possible technological development within a standard.

The main difference of V3 compared to the previous one is that it allows to overcome the aforementioned problems, it concerns the relationship between information and data: in V2 the only rules concerned sequences of segments and the possible presence of the values within the composites, in V3 a model was given to the information structure of the n, adopting, as anticipated, an Object Oriented (OM) approach and based on the principles of Unified Modeling Language (UML).

This change increases the detail, clarity and accuracy of specifications, favoring both the actors who preside over the development of the standard, both the developers and they must implement the standard itself. Each information represents an object that possesses its own attributes and maintains relationships with other classes (i.e. other types information). This data model is known in the literature as the HL7 Reference Information Model (RIM).

Another big difference concerns the format in which the data is transported, since we moved from the use of delimited text in V2 to the use of XML, a much more suitable, appropriate and standardized language for sharing and data transmission.

2.3.2.1 Reference information model

The RIM is the information model, is the source from which all standards of the HL7 V3 family get the information content model.

An information model serves to makes the meaning of the wanted information explicit. An abstract information model is defined within the RIM, not its concrete format. It expresses classes and properties, such as attributes, constraints, relationships and states, of the classes of information to be

represented. Thus it associates a semantic content to the data contained in a message which is sent to an application.

The information model has an object structure, therefore there are UML diagrams that schematize it (Figure 2.6):

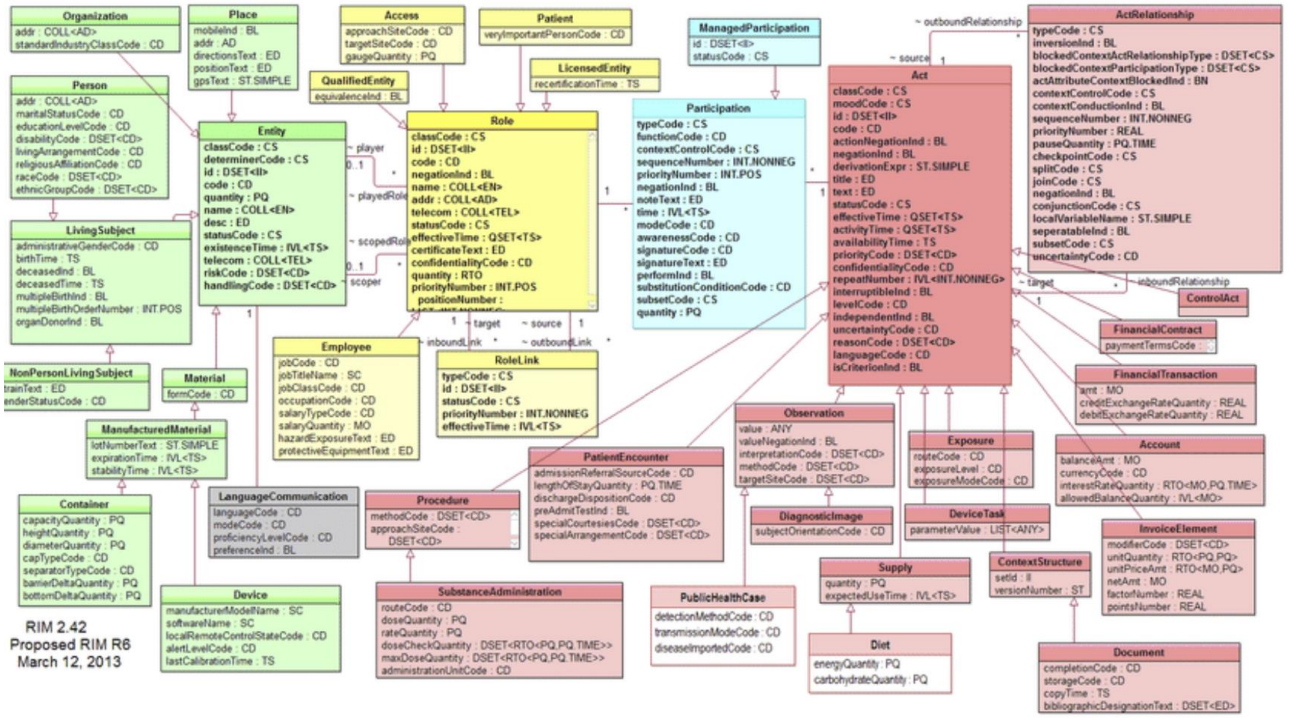

Figure 2.6: UML ofl HL7 V3 RIM

The fundamental concept is that of foundation classes, that is 6 components through which all the various possible interactions in a clinical context are modeled.

These components are:

- Entity: it represents all possible actors (physical or instrumental) that can act. In the UML this class (and all the ones below) is represented in green color (Figure 2.7)
- Act: it represent all the possible actions that can be performed by entities. This class (and the set of those below) is represented in pink 8Figure 2.7)
- Role: they represent the roles that entities can play. There Role class (and the set of those below) is represented in yellow (Figure 2.7)
- Participation: it indicates how staff in a certain role must participate in one certain action. For example, Dr. (Role) Mario Rossi (Entity) has the role of referent (Participation) for ultrasound scans (Act). This class is indicated in light blue color (Figure 2.7)

- ActRelationship: it represents the set of minor actions in which an Act can having to be broken down. In the standard they are indicated in light pink color (Figure 2.7)
- RoleLink: it indicates whether some roles exist in the organization as they are connected to other roles. For example, a doctor can only practice in clinic X if he is one employee. RoleLink objects are indicated in light yellow color (Figure 2.7)

The complete relationships between these fundamental components are illustrated by the following diagram illustrating the data meta-model:

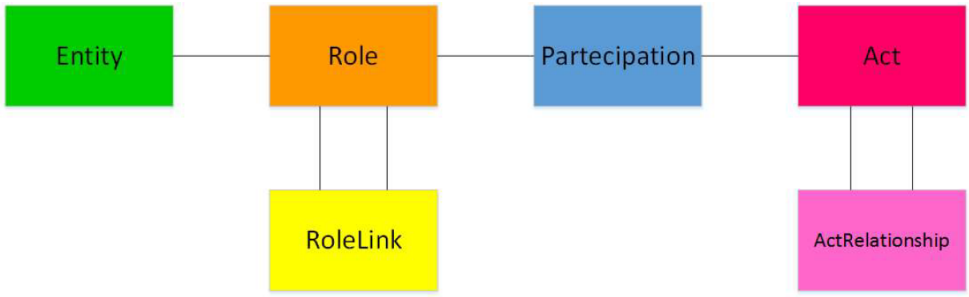

Figure 2.7: RIM Meta-Model

It can be verified that the meta-model corresponds to a subset of the classes shown in RIM's complete UML schema (Figure 2.8).

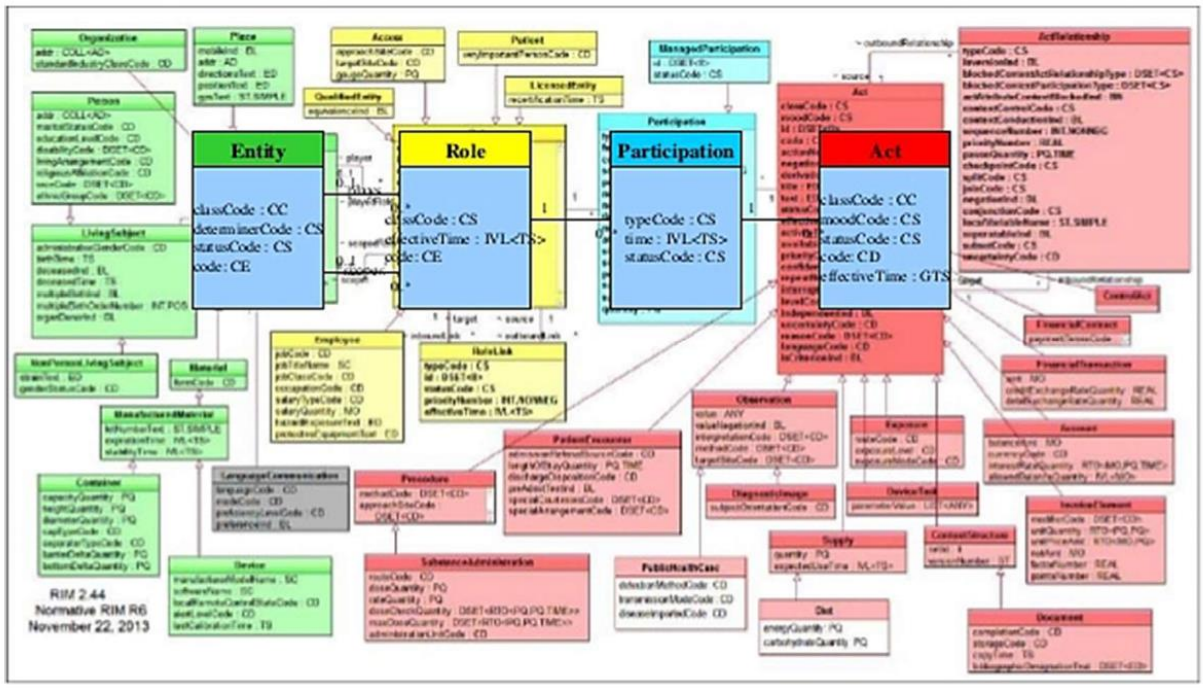

Figure 2.8: Correlation between the Meta-Model and a subset of the classes in the RIM UML schema

In order to derive another model from this basic model, the following constrained have to be considerate:

- All classes derive from one of the 6 types above and keep the coloring
- The classes deriving from Entity, Act and Role are represented by rectangles
- Classes that derive from ActRelationship and RoleLink are represented by arrows

In the context of HL7 V3, two real examples of data models derived from RIM are the D-MIM and the R-MIM:

- Domain Message Information Model (D-MIM): It is a subset of the RIM that includes a set of classes and attributes that can be used to create messages in a domain specific. A domain is a way to represent a specific area of healthcare. The domain name must clearly convey some information to both developer and reader.
- Refined Message Information Model (R-MIM): It is a subset of D-MIM (therefore transitively of the RIM) used to express the information content of a message or a set of messages within a particular Topic. A Topic is a subdivision of domain that allows you to organize it in such a way allow the reader to quickly identify the context in which he is interested. The reader must have a clear idea of the content of the document by looking at the title of the Topic and that of the domain. The R-MIM is also used to represent the information content of structures abstract messages called Hierarchical Message Definition.

2.3.3 FHIR

The FHIR is the last standard proposed by HL7, which has been set up to inherit the best features from its predecessors. FHIR can be used as a tool to exchange information, both "stand-alone" and together with previous versions. One of the main features of FHIR is to be simple to implement, using concepts and tools which are widely used in computer science. FHIR, like the HL7 V3, is object oriented and its main concept is "resource". Every real world entity is a unique "resource". In V3 different models can represent the same concept, for example there are ten different ways to represent a "patient". FHIR identifies the patient in a unique way. Multiple profiles can be created, but they all have the same pattern and the same serialization. FHIR allows two different formats: XML and JSON [33].

The resources are an extremely varied set of objects. All resources have three components in common:

• A way to define the resource or to represent it, in a "human." readable " starting from established" data types ".

• A set of metadata, that is a set of information such as the id or the last update

• A "human readable" part where the content of the resource is explained

Further details on FHIR implementation can be found in link https://hl7.org/fhir/implsupport-module.html.

2.3.4 Standardized medical vocabulary

In recent years, due the development of technology, data sharing has become simpler in terms of speed and allows greater ease of communication. To ensure good data sharing, therefore, the need for one was born common and standardized terminology, flexible and extensive dictionaries, covering all requirements in the medical-health landscape and sufficiently rigid not to give rise to errors of interpretation. In the medical and biomedical domain, the coding of information and standardization of terminology are preconditions and indispensable in order to guarantee the effectiveness and efficiency of the therapeutic paths and the administrative procedures connected to them. The need to use a unified and interoperable language, which favors the circulation of information and the communication between the various subjects operating in the health sector is, in fact, by now indispensable in a field, such as the medical one, in which terminological consistency, uniqueness and clarity have become of fundamental importance for the health of the citizen and, consequently, for the efficiency of the health system.

2.3.4.1 LOINC

Logical Observation Identifiers Names and Codes (LOINC) [34] is a standard international coding and unambiguous description of clinical and laboratory observations, which aims to facilitate the sharing and exchange of diagnostic investigation results between information systems of different health facilities.

The LOINC standard was created in 1994 by the Regenstrief Institute, organization non-profit of medical research associated with the University of Indiana (USA), and by LOINC Committee. Translated into 9 languages and 18 language variants, LOINC is now used in more than 150 countries in the world. A database is available to facilitate the exchange of data medical-health and research type. The last update was made in August 2022 (ver.2.73). Updates are every six months. The consistency is around 90,000 terms. Downloadable from the net in Access format with accessories and documentation (Relma6.12).

According to the provisions of art. 17 of Law Decree 69/2013, on March 31, 2014 the Agency for Digital Italy has published guidelines for the preparation of the plans FSE. In them, as well as in the DPCM on the FSE prepared by the Ministry of Health to be issued soon the use of LOINC codes is

mandatory for the unique identification of the exam carried out within the report documents in HL7 CDA2 format. LOINC, AIC, ICD-9 are databases and universal standards that provides a list of names and ID codes for the identification of results in laboratory and clinical tests.

2.4 Architectural approach

The service-oriented architecture (SOA) is an architectural approach based on the use of web services. A service is a piece of functionality made available by a service provider in order to deliver end results for a service consumer. These services communicate with each other: the communication can involve simple data passing or it could involve two or more services. A service consumer sends a request to a service provider, which returns a response containing the expected results. SOA emphasizes on breaking business processes into smaller blocks (services), thus addressing issues related to re-use, maintenance and integration [35].

SOA is increasingly used as an integration paradigm for the Healthcare Information Systems (HIS). Healthcare organizations demonstrate ongoing efforts to reduce costs and improve the quality of their services through system integration. The emphasis on standards based interfaces is a critical success factor for SOA.

The number of interfaces grows exponentially as the number of connected systems increases, rising the expense for interface design, development and maintenance. The SOA paradigm adoption reduces the number of point-to-point interfaces, thus reducing costs. Another advantage of SOA approach is the facilitation in software design and implementation, due to the decomposition of complex problems into smaller ones [36].Software reusability is also a crucial point that can be achieved using Service Oriented Architecture, reusing existing IT resources and improving adaptability to new requirements. Among the recognized benefits of SOA, the improvement in data quality is the most important, especially in the medical field. The enhanced interoperability allows to produce more accurate and up to date information that are essential for the healthcare decision-making process [37].
Considering described the benefits, a number of organizations have adopted the SOA approach in health care environments, and in specifically in CDS. A literature review about it has been carried [38],which highlight six general architectural themes:

1. point to point
2. enterprise service bus
3. service registry

4. clinical guideline engine
5. rule based engine
6. service choreography and orchestration

This review shows that all this architectural approaches can coexist within a SOA based implementation of a CDS.

Contract standardization and scalability are features for which SOA integration can be seen as a process that enables interoperability. According to HIMSS, interoperability is "the ability of different IT systems and software applications to communicate, exchange data, and use the information that has been exchanged" [39]. Interoperability has are three levels:

- *Foundational interoperability:* it allows data sharing, so that data sent by one system can be received by another system, but it does not imply that the receiving system can interpret it.
- *Structural interoperability: it* is an intermediate level that defines the format of the data exchange and it focuses on the packaging of the data into standard messages. Specific standards, such as Health Level 7 for the healthcare field, provide guidance on how messages should be structured.
- *Semantic interoperability*: it is the ability of two or more systems not only to successfully exchange information, but also to meaningfully interpret the information exchanged. It is granted only when both systems refer to a common information reference model. In healthcare, the most known and used information model is Reference Information Model (RIM) of HL7.

A SOA architecture does not guarantee complete interoperability. Semantic interoperability is essential for SOA architectures to grant consistency in the data exchange among service providers and service consumers.

2.4.1 Healthcare Services Specification Project

The HSSP was formed in 2005 within a collaboration among HL7 and the OMG standards groups [40]. The objective of the HSSP project is to produce standards that define the services' interfaces, functions and behavior supportive of the healthcare sector based on SOA principles. The HSSP aims at the standardization of services involved in health processes, facilitating the development of a set of standard interfaces. The HSSP standardization cycle produces two specific levels of service: Service Functional Model (SFM), managed by HL7 International and the Service Technical Model (STM), managed by OMG. The SFM is a specification of the functionality of a service; it does not specify any technology or platform because it is implementation-independent. The "business

capabilities" and "profiles" sections provide the core normative service description. Each business capability describes a specific action that the service must perform, resulting in one or more operations. A set of profiles are defined to cover specific functions (functional profile), semantic information (semantic profile) and overall conformance (conformance profile). The functional profile consists of a list of all the operations defined within the service; the sematic profile defines the meaning of the entities and their properties, and could provide cross-references to the RIM based domain models; the conformance profile is a machine testable specification of all conformance issues. As shown in the diagram in figure 2.9, after the development of a SFM, the next step is the adoption of the SFM as a Draft Standard for Trial Use. To be adopted as a draft standard, the HL7 specification has to be presented to the HL7 national membership for the ballots. After the adoption of SFM as an HL7 draft standard, a Request for Proposals (RFPs) for a technology-neutral Platform Independent Model and one or more technology-specific Platform Specific Models (PSM) for the service are generated under the supervision of the OMG group. The final step is the revision of the adopted standards based on real implementations. Presently, there are some HSSP products for which SFM and STM has been developed.

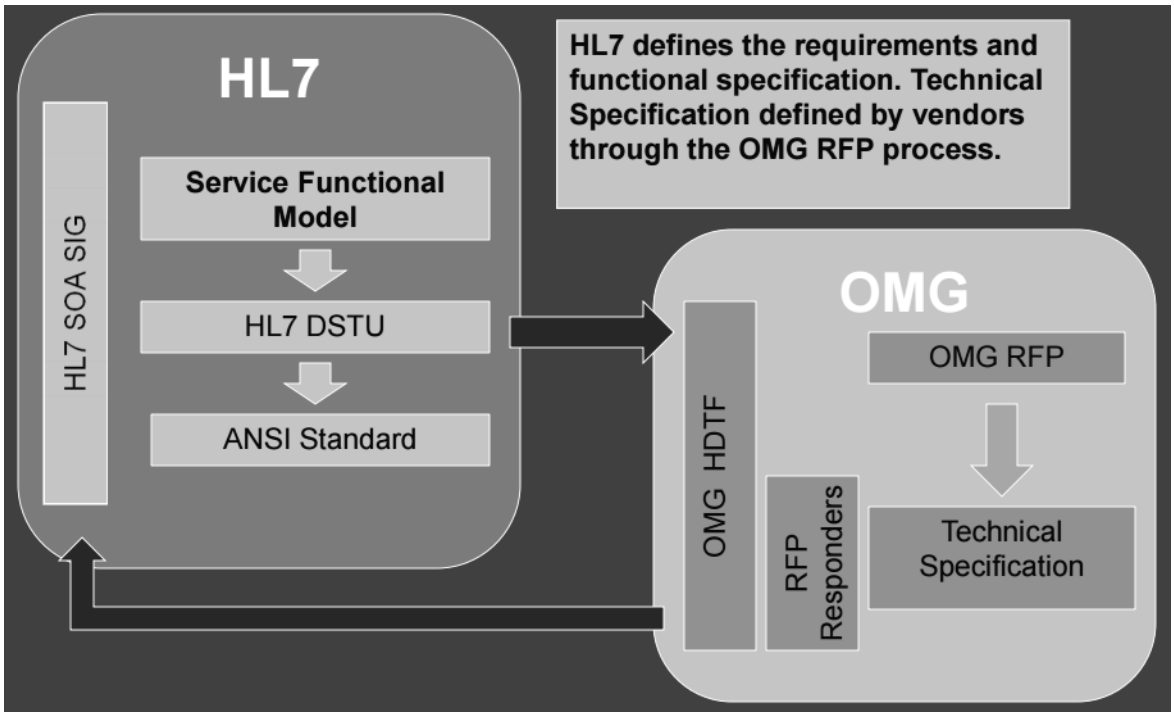

Figure 2.9: HSSP standardization cycle. Two specific levels of service are defined: the Service Functional Model (SFM) is managed by HL7 International and the Service Technical Model (STM) is managed by OMG group.

2.4.1.1 Identification and cross-reference service

The Identification Service (IS) also known as the Identification and Cross-Reference Service (IXS), manages the identifying information for different kinds of entities, such as people, organizations, devices and others. It provides means for managing, defining and updating identities and systems that share a standards interface to maintain a common description of each entity. The SFM specifications refer mainly to patients as entity, because it is the most common entity that generates problem to a wide audience, but similar functionality and scenarios are relevant also to other types of entities. The main problem on which this standard is focused is the merging of all the identification codes (IDs) that are assigned to a person by each healthcare facility during lifetime. Having a standard for the process of identification of a patient considerably improves the quality of care.

2.4.1.2 Retrieve, locate, update service

The Retrieve, Locate, Update Service Release 1 (RLUS) provides means for interacting with a system that exposes the data of interest, providing a standardized way of location, update, and retrieval of that content. The RLUS objective is the definition of service interfaces for the creation, registration, update, search, discovery, retrieval and query of clinical and health resources. The main operations involved are to locate, get, list, put, initialize and discard resources.

2.4.1.3 Decision support service

The Decision Support Service Release 1 (DSS) provides decision support to clinicians based on real-time patients' data. Decision support systems could be highly effective and improve clinical practice. A DSS contains many "knowledge modules", which are able to drive machine-interpretable conclusions about a patient using on his/her data. When requesting for an evaluation, the client specifies the knowledge modules to be used, and provides the patient data that are required by the knowledge modules. The DSS returns the evaluation made on the patients in a format that is pre-defined for the used knowledge modules.

2.4.1.4 Common Terminology Services Release 2

The Common Terminology Services Release 2 (CTS2) is a terminology service that provides a standardized interface for the use and maintenance of terminologies. The service interface allows the query, definition and modification of the terminology components, establishing a common model. It

specifies the interactions between terminology providers and consumers, managing revisions, corrections and extensions through versioning.

2.5 Knowledge representation in Clinical Decision Support System

The Clinical Decision Support System (CDSS) relies on data stored in a database to drive conclusions about a patient's problem basing on a knowledge base. The type of logic to be used derives from the kind of knowledge base implied. Ruled-based CDSS use knowledge acquisition tools that facilitate the creation and maintenance of a knowledge base made of condition–action rule templates [41].

The knowledge used as basis for decision support should have an adequate scientific evidence, and any deficiency in the quality or relevance of it could affect the CDSS effectiveness. The knowledge basis should be extracted from the research literature, guidelines and up-to-date practice-based sources [42]. Once extracted from the most appropriate sources, most frequently from clinical guidelines, knowledge has to be made easily accessible in machine interpretable format to be computationally digested by the software. A knowledge management system is therefore needed to extract, maintain, update and share computer interpretable evidence-based knowledge.

2.5.1 Computer interpretable clinical guidelines

Clinical Practical Guidelines are "systematically developed statements that can be used to assess the appropriateness of specific health care decisions, services, and outcomes", as defined in 1990 by the Institute of Medicine [43].

According to [44] clinical guidelines should accomplish 5 tasks:

1. Making of decision: one of the main purposes of the clinical guidelines is the support to be provided to physicians in making a decision
2. Sequencing of actions, that is to support the structuring of actions and decisions and, therefore, suggest the temporal order of the actions or the possible sequence
3. Setting of goals: indicates the ability of the physician to identify, through the guideline, the goals to be pursued in applying a specific treatment to a clinical case

4. Interpretation of data: the application of a guideline to an individual always requires customization of the abstract and general concepts described
5. Refinement of actions.

These tasks are interdependent, and the links among them are shown in figure 2.10: the continuous line arrows indicate the sequence of actions and decisions, the arrows in dashed line indicate the choice between different alternatives, while the rounded arrows indicate data flow.

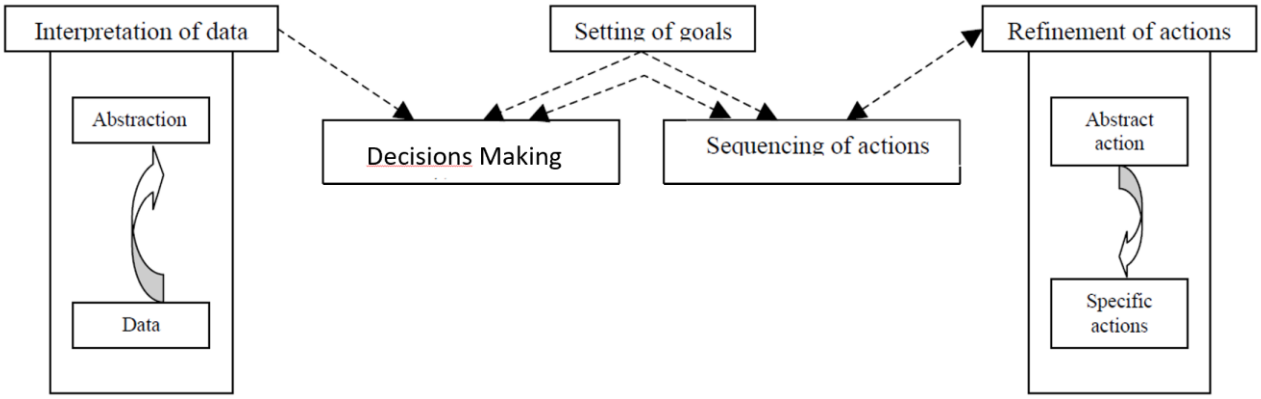

Figure 2.10: Schema representing the tasks that a clinical guideline have to accomplish. These tasks are interdependent: the continuous line arrows indicate the sequence of actions and decisions, the arrows in dashed line indicate the choice between different alternatives, while the rounded arrows indicate data flow.

Computer-interpretable clinical practice guidelines (CIGs) are text-based clinical guidelines converted to machine executable CDSS rules through the use of a guideline representation model. A guideline representation models are representation languages and frameworks that can be used to model guidelines and protocols in a computer interpretable and executable format.

2.5.1.1 The Guideline Interchange Format

The Guideline Interchange Format (GLIF) was created by the InterMed collaboratory, a joint project of biomedical informatics groups at Harvard, Columbia, and Stanford universities, to serve as a common representation format for CIGs .[45]. The first version of GLIF was rather limited and was not widely disseminated.

GLIF2 [46] was designed to support guideline modelling as a flowchart of structured steps which represented clinical actions and decisions. GLIF2 was published in 1998 and consists of two main parts: a model to GLIF objects and GLIF syntax.

The GLIF2 model allows specification of a guideline as a flowchart of steps ordered temporally. The steps represent actions or clinical decisions and, at the same time, are used ramifications and synchronization step. Four types of steps are considered:

1. Action steps: specify clinical actions that has to be undergone during the care process
2. Decision steps: could be conditions or branches
3. Conditional steps: contains a condition, or criterion, which is a logical statement that may be evaluated to true or false
4. Branch steps: direct flow to multiple guideline steps

GLIF2 presented a few limitations for example, some important attributes did not have a structured representation and some concepts and flow-control constructs were missing.

GLIF3 is the last revision that overcomes the previous difficulties. Specificaly, object-oriented expressions and query language has been added, the flow-control has been improved [47]. The GLIF3 model consists of classes, their attributes, and the relationships among the classes, all of which are necessary to model clinical guidelines.

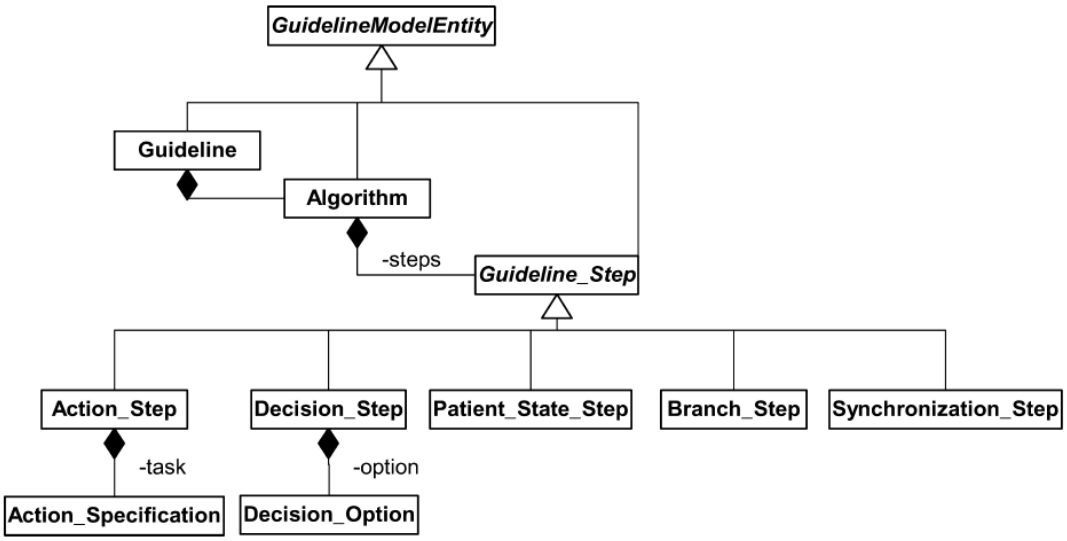

Figure 2.12: A high-level view of the major classes in GLIF. The lines between the classes denote relationships: a diamond-shape arrowhead indicates an aggregation or containment relationship, and a triangle shape indicates inheritance.

GLIF3 supports representing clinical guidelines in three levels of abstraction:

1. Conceptual level: the guideline is represented as a flowchart.
2. Computable level: completeness and logical consistency of the guideline can be checked. The expression syntax, the medical actions and the algorithm flow are defined.

3. Implementable level: the guideline is ready to be incorporated within environments of institutional information systems.

Action and decision classes of the GLIF ontology reference patient data items and medical concepts. These concepts are formally defined by standard controlled vocabularies (e.g., UMLS, LOINC, SNOMED CT) and standard medical data models. A reference information model defines the basic data model for representing medical information and it is essential for guideline execution and data sharing among different applications and different institutions. The default reference information model that GLIF3 supports is HL7's RIM version 1. Core GLIF defines how medical data items are structured and how they relate to medical concepts.

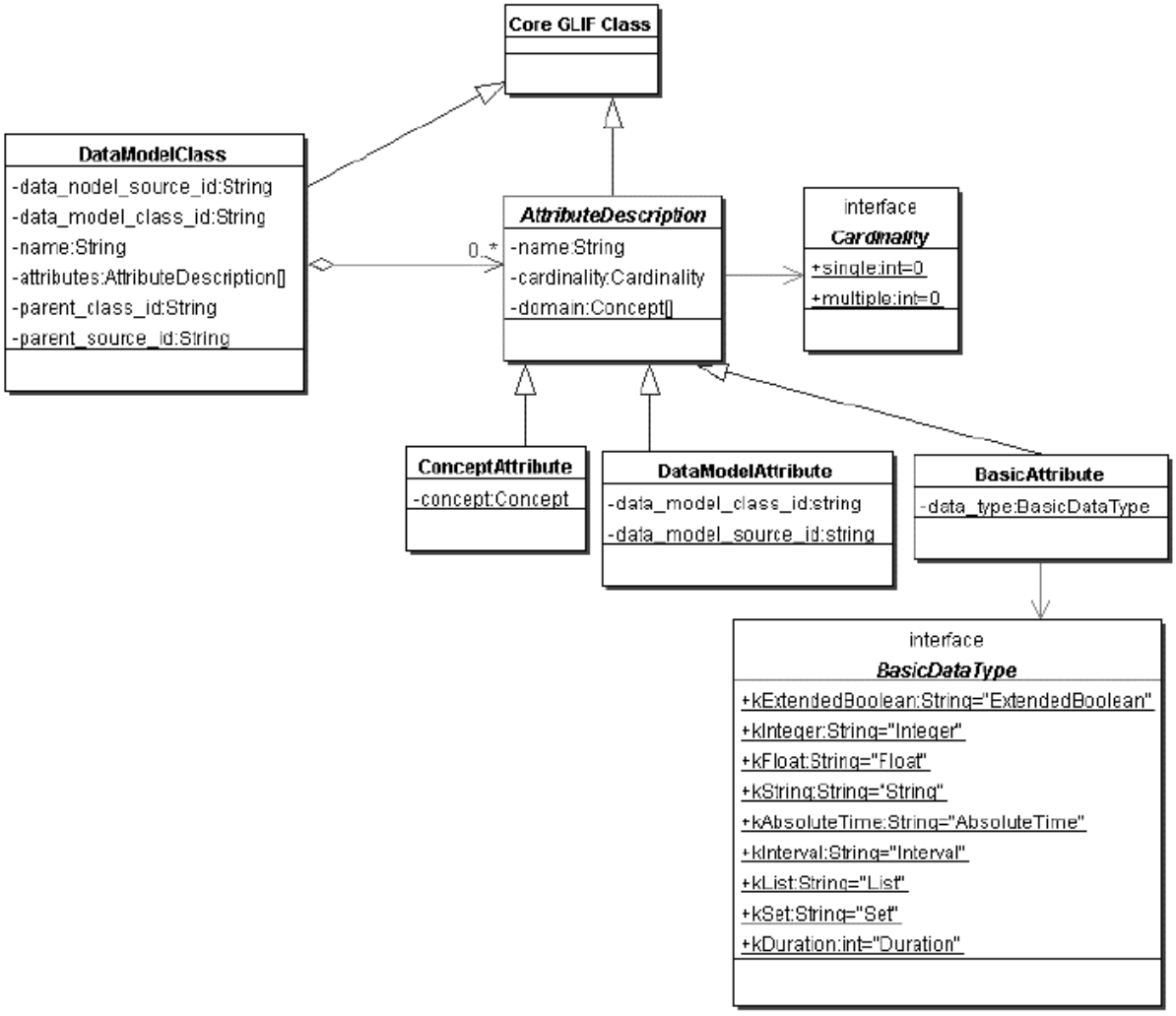

Figure 2.13: Core GLIF class diagram

The HL7 RIM class diagram is shown in figure 2.14.

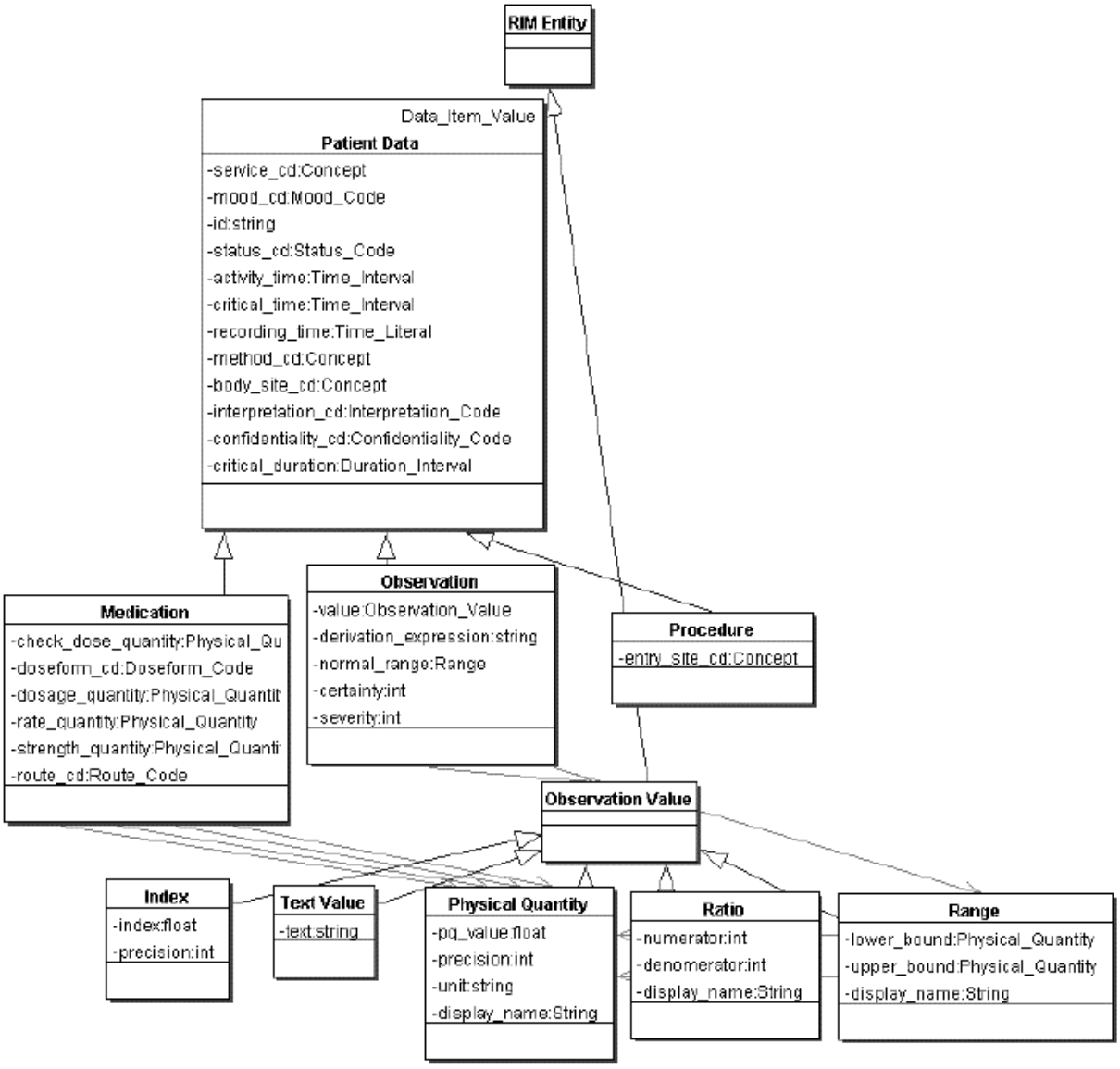

Figure 2.14: HL7's RIM class diagram

The Guideline class of GLIF ontology is used to model clinical guidelines and sub-guidelines. GLIF's guideline class specifies the algorithm, which is a flowchart of guideline steps, maintenance information such as author, guideline status, last modification date, and version. The intention of the guideline, the eligibility criteria, didactics, and the set of exceptions that interrupt the normal flow of execution are specified too. The guideline also defines patient data items that are accessed by it and parameters that the guideline passes in and out to other sub-guidelines. Figure 2.14 reports this information.

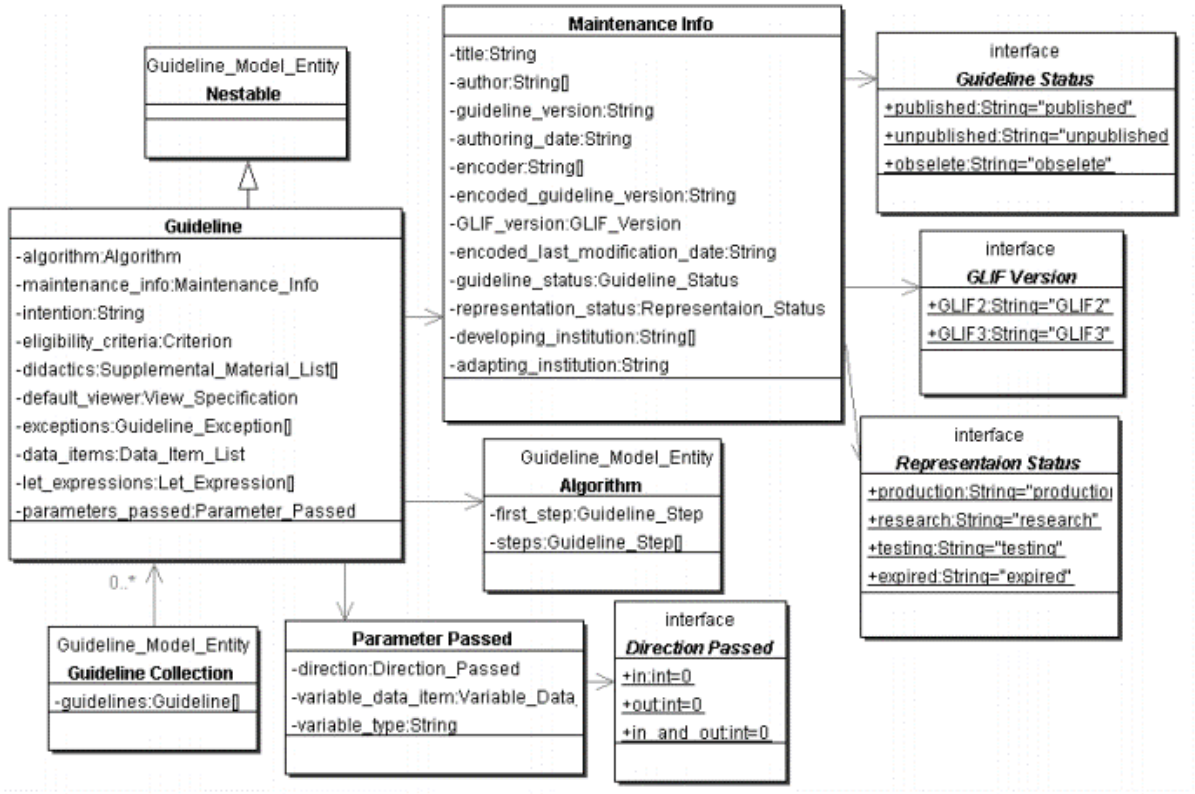

Figure 2.15: The GLIF guideline package

2.5.1.2 GELLO

GELLO is a standard object oriented query and expression language for clinical decision support [48]. It is a language to write expressions and make queries on medical data. GELLO expressions can be shared among institutions with different systems without the need of rewriting. GELLO programs refers to an environment that contains a list of predefined classes which can be used with their properties and methods (attributes and operations).In general, the data model supplied to the GELLO program will have a number of classes which represent components of the data model.

GELLO expressions can be embedded at any point where decision rules, eligibility criteria, patient state specifications or guidelines are needed. For example, decision points in the GLIF flowchart runs automatically by using GELLO to evaluate computable decision criteria on patient's loaded data. GELLO is compatible with the Reference Information Model RIM of HL7.

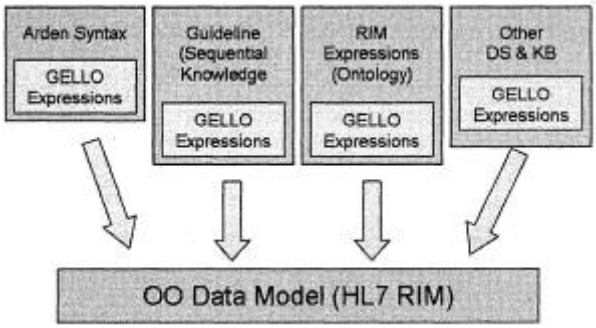

Figure 2.17: GELLO and its relation to Arden Syntax, GLIF, RIM and other DSs and KBs. GELLO query and expression languages can be embedded into various tools to provide the mechanisms for access and manipulation of Object Oriented data.

There are two phases in embedding GELLO code into decision support system: the pre-execution phase, which consists in parsing and compiling, and the execution phase, which consists in requesting and evaluating patient's data. The execution phase consists of three steps, which are reported in figure 2.17 In the first step, GELLO expression is considered. If it is an evaluation then it goes to step three, while if it is a request of patient's data it goes to step two. In the second step, the expression is an internal call to the DBMS requesting information about a patient. The DBMS is an intermediary database compatible with HL7 RIM (such as vMR) that handles the request, retrieves the information and returns it to the application. Ad-hoc mapping software extracts data from the institution database and stores it into the DBMS. Institution's databases where patients' data are stored are organized in specific ways that may not be compatible with other institution's data organization. In the third step, if all needed information is available, the engine evaluates the expression and returns the result to the application.

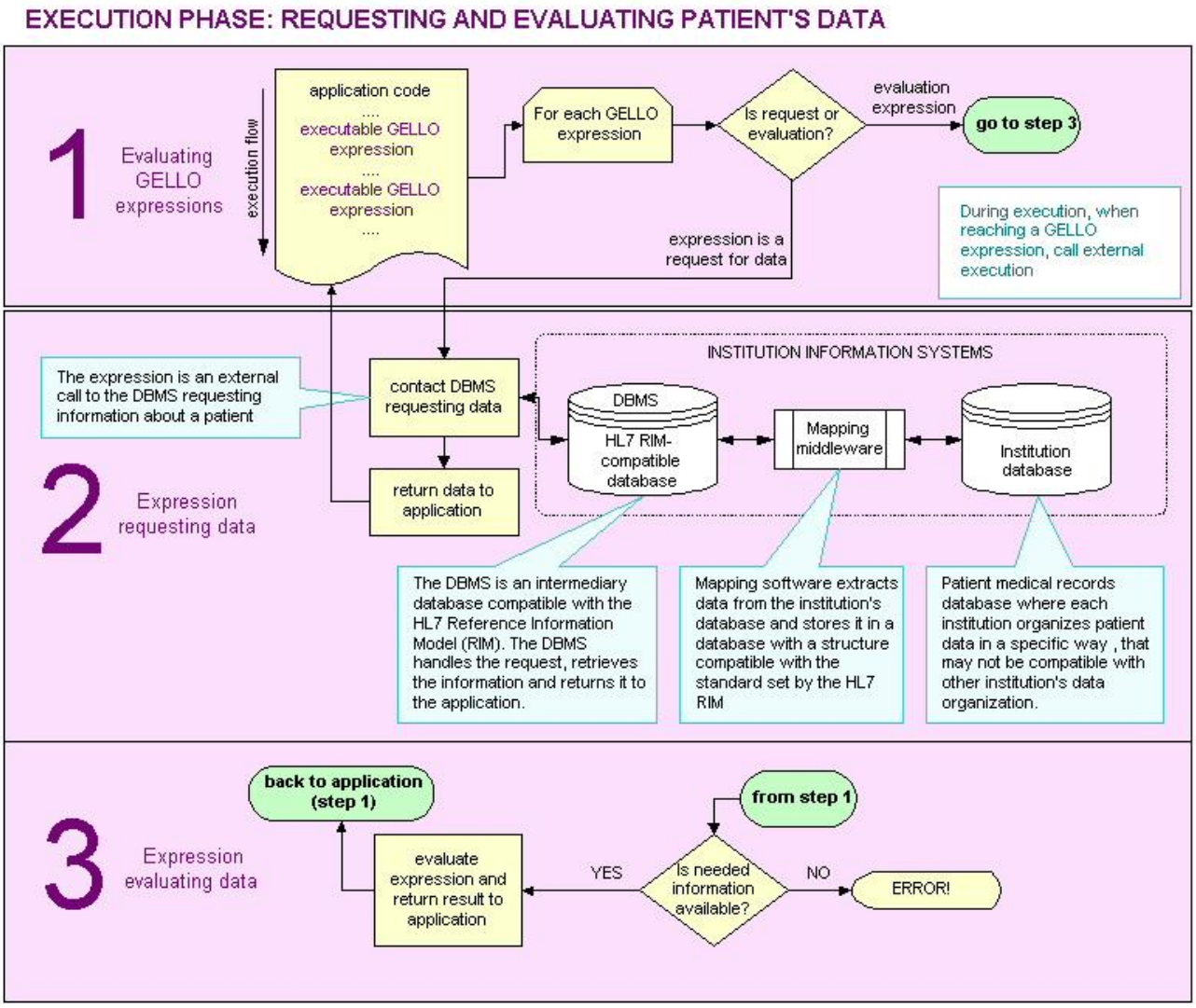

Figure 2.18: The execution phase of GELLO consists into three steps: evaluating GELLO expressions, requesting data and evaluating data.

2.5.2 Standards for CDSS: HED initiative

Health eDecision (HeD) is an initiative of the Office of the National Coordinator‘s Standards & Interoperability Framework [52]. HeD does not aim to create a new standard, but its intent is to identify, define and harmonize already existing standards involved in clinical decision support field. The main standards considered are:

- **HL7 Virtual Medical Record (vMR)**, a data model for representing patient’s data that are analyzed and/or produced by Clinical Decision Support engines
- **HL7 CDS Knowledge Artifact**, for knowledge artifact specifications

- **HSSP HL7 Decision Support Service (DSS)**

This initiative actually supports two general use cases. The first use case “CDS Artifact Sharing” is about knowledge artifact exchange and it specifies how to structure medical knowledge in a sharable and executable format. The second use case “CDS Guidance Service” relates to the exchange of information that allows the delivery of the results derived from the execution of clinical decision support, focusing on how a clinical decision support system receives data and returns conclusions and recommendations.

2.5.2.1 vMR

The vMR is a standard for the representation of medical knowledge for CDS developed by the HL7 group. It is a RIM based data model that represents the data that are analyzed and/or produced by CDS engines, thus allowing interoperability between different CDS and medical data sources.

González-Ferrer et al. assert that the vMR model is bi-dimensional, in which one dimension represents the type of clinical information (Procedure, Observation, Problem, Substance Administration, Goal, Encounter) and a second one the workflow moment (Proposal, Order, Event) [53].

The vMR can be considered a simplified representation of the clinical record that is suitable for a CDS knowledge engine to directly manipulate in order to derive patient-specific assessments and recommendations. With respect to the CDA, it avoids multiple nesting of concepts. It uses a simplified version of the HL7 version 3 data types release 2, with a particular attention to the management of the null flavors. It employs a more intuitive representation of concepts, using alternate methods to express the concepts of mood codes, negation indicators and inversion indicators.

The vMR class diagram is represented in figure 2.19. Substantially, the vMR class can refer to a particular template, among those listed in the draft standard for trial use (DSTU) “HL7 Version 3 Standard: Virtual Medical Record for Clinical Decision Support (vMR-CDS) Templates, DSTU Release 1”. The class vMR has an EvaluatedPerson type attribute, which is a Person (inherits from Person class) which, in turn, inherits from Entity class. The EvaluatedPerson can have an indefinite number of ClinicalStatement attributes. The ClinicalStatement class is a concrete class that can be used as is or specialized as needed into more specific clinical statements, such as ObservationResult, SubstanceAdministrationEvent and Problem.

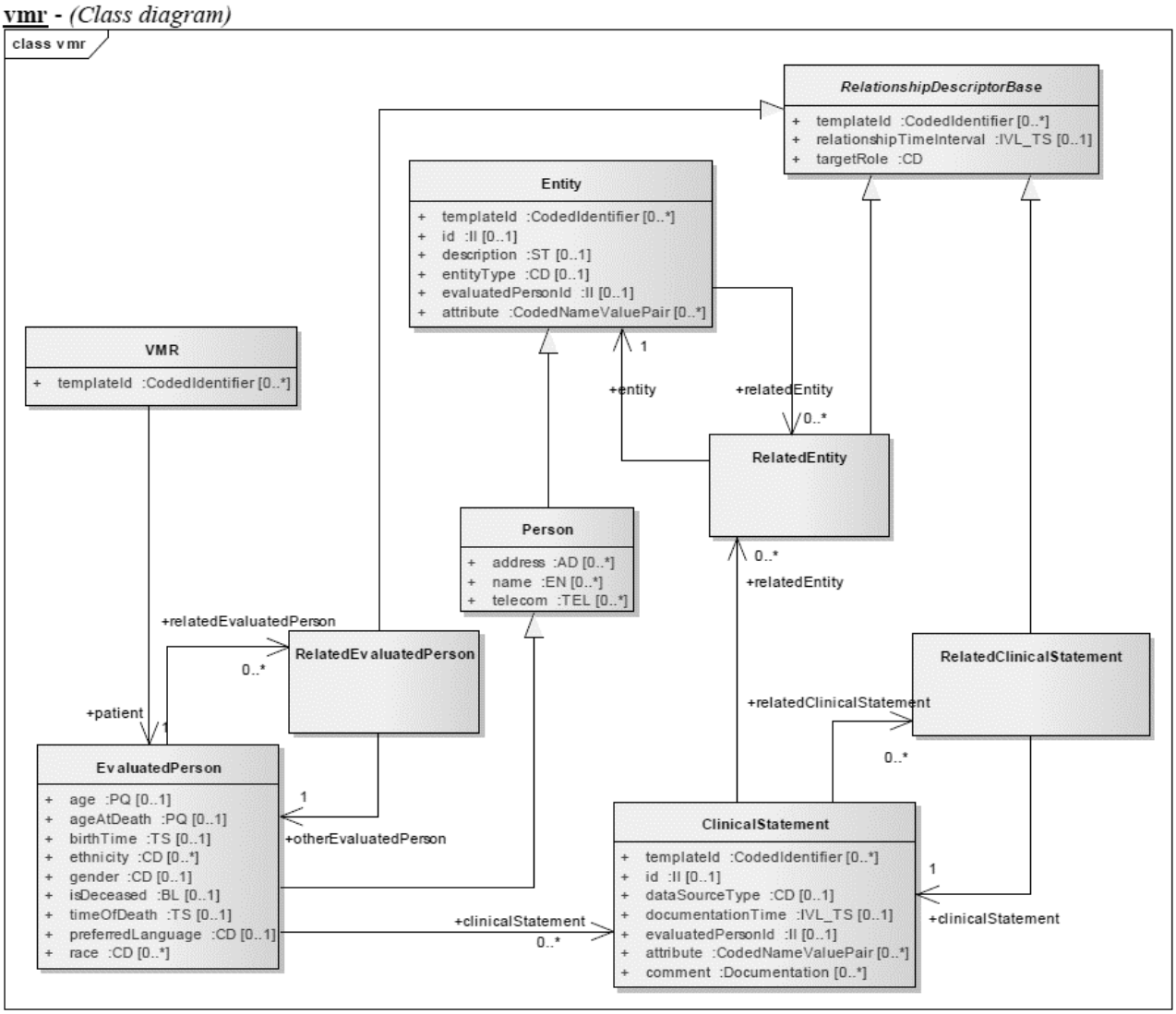

Figure 2.20: vMR class diagram

2.6 Machine learning

The widespread adoption of systems based on AI led to the conduction of several research studies involving ML-based methods in the cardiological scenario, e.g. to predict the mortality and hospitalization in heart failure subjects[56]. However, in order to do that a great amount of clinical data is required. Ad hoc clinical data collection through Randomized Controlled Trials (RCTs) is expensive from a costs and resources point of view and it also takes much time to execute. In addition to that, usually, RCTs are designed to answer a narrow hypothesis in a highly targeted population and this can lead to knowledge gaps [57]. Thus, RWD became an appealing data source. RWD are data

which are collected in the routine clinical practice through a variety of sources such as EHRs, administrative flows related to hospital pharmacies, observational registries, etc [58]. The use of RWDs in research represents a huge and important change, mainly supported by the widespread adoption of EHRs that creates a framework for collecting and analyzing health data. Anyway, health data is only useful if it can be transformed into meaningful information and this requires high-quality datasets, communications between IT systems and standard data formats that can be easily processed. However, most medical data today lacks interoperability, data is often stored in incompatible systems and thus makes it difficult to exchange, analyze and interpret data [58]. Fully exploiting the digitalization of medicine requires an interconnected data infrastructure with fast, reliable and secure interfaces, international standards for data exchange, medical terminologies that define unique vocabularies for the communication of information. Interoperability is essential for advances in digital health and must be a prerequisite for most innovations which are being planned for future medicine. In addition to the problem of dealing with RWD, the access to health data is strictly subjected to privacy laws and permission should be validated by an ethics committee. Due to all these reasons, many researchers decide to conduct their studies on publicly available databases, such as repositories of healthcare industries and third-party data sources, in order to have access to relevant data in a short time [59]. Examples of these data sets are: Cleveland Heart Disease Dataset, UCI machine learning dataset [60], [61].

During the second and third year of my PhD I analyzed the applicability of an AI pipeline starting directly from the RWDs collected with our system. My main challenge was to demonstrate that good results can be achieved starting with interoperable and well-structured RWDs. In the following paragraphs the techniques and methods of ML that have been used are described.

2.6.1 The regression

Regression analysis is one of the most widely used statistical techniques. Its task is to explain the relationship between a variable Y (continuous) said response variable, dependent, and one or more independent variables called regressors (X1, X2, ... Xk). The regression function can be expressed as:

$$Y=f(X_1, X_2,\dots X_k)+\varepsilon \tag{2.1}$$

which through the component f (X1, X2, ... Xk) indicates the existence of a functional link between the dependent variable Y and the regressors, and defined as a systematic component. To this

component a second component adds called accidental, or random, which unlike the first cannot be explained by the regressors, and must be therefore brought back to chance, that is to say to different, external causes not considered by the regressive model.

The functional link is often represented by a linear type function and therefore yes speaks of multiple linear regression or linear model can be formulated as follows:

$$Y = \beta_0 + \beta_1 X_1 + \ldots + \beta_k X_k + \varepsilon \qquad (2.2)$$

where β_0 is known as the known term, β_1, ..., βk are the regression coefficients and, together with the variance of the error, are the parameters that characterize the model and must be estimated starting from the observations that make up the sample. Where the relationship between the variables do not appear linear, the regression models allow to carry out some specific transformations with the aim of linearizing the relationship. This is the case with the logistic regression, where logarithms are used to transform the relationship.

Finally, when the response variable Y is not continuous, in the case of dichotomous variables (logistic regression) or counting variables (Poisson regression), it is customary to use a generalization of the linear model.

2.6.2 Logistic regression

When Y is dichotomous, and coded as 0 -1, its distribution is binomial. The estimate of the dependent variable, therefore, must vary between 0 and 1 and not between - infinite and + infinite such as linear regression estimates. In this case, then for values which are very high in X (or very low if the relation is negative) the value in Y is very close to 1 e must not exceed this limit. The same happens near 0. In practice, the curve which represents the relationship between X and Y is logistical and non-linear. In logistic regression the dependent variable identifies membership of a group.

The values that are assigned to the different levels, in order to identify one group rather than another, are assigned in an arbitrary way. The result of interest the logistic regression model, therefore, is the probability that a given subject belongs to at least one of the two groups. Despite this, the values assigned to the levels, even if arbitrary, influence the result of the analysis, and that is why it can sometimes be useful to replace the probability with the corresponding odds.

Odds is a way of expressing probability through a relationship. It is calculated as the relationship between the frequencies observed in the different levels. Once the frequencies are defined, it is possible to trace the relative frequencies, or percentages, of the two levels. Also, after having calculated the odds, executing its natural logarithm obtains what is defined as logit. "If we compare

the distribution of frequencies, relative frequencies, odds and logits we can see how all these statistics provide the same information although with mathematically different values. When the categories successes (Y = 1) and failures (Y = 0) are equally probable, the relative frequencies are equal to 0.5 for both categories of Y, the odds are equal to 1, while the logits are equal to 0. When the number of successes is greater than the number of failures, the relative frequencies the odds assume values higher than 0.5 for category Y = 1 and lower for category Y = 0 take values greater than 1, while the logit values greater than 0. Finally, when the number of successes is less than the number of failures the relative frequencies assume values lower than 0.5 for category Y = 1 and higher for category Y = 0, the odds they take on values less than 1, while the logit values are negative. In practice, while the frequencies relative have a range of variability that goes from 0 to 1, the odds have a range of variability ranging from 0 to plus infinity, while logits can range from minus infinity to plus infinity.

In this case, the non-linearity of the relationship between the variables does not allow to apply the OLS method without first applying opposite transformations that make the relationship, and in particular in terms of parameters. It is therefore necessary to proceed with the logarithmic transformation of the dependent variable.

To express the relationship between independent and dependent variables in linear terms we start from the following formulation in which the expected value of the dependent variable is la chance:

$$(\hat{Y} = \mu_Y = P_{(Y=1)}), \tag{2.3}$$

so the probability of Y = 1 as a linear function of X becomes:

$$P(Y=1) = \alpha + \beta X \tag{2.4}$$

As mentioned above, this model is not adequate. The values of probabilities have an admissibility range from 0 to 1, while the term $\alpha + \beta X$ can assume values ranging from less infinite to more infinite. To solve this problem yes apply as a first step the exponential transformation to the right-hand term of the function that becomes:

$$P(Y=1) = e^{\alpha+\beta X} \tag{2.5}$$

2.6.3 Regression models

Starting with the simplest case, single-variable linear regression is a technique used to model the relationship between a single independent input variable (function variable) and an output dependent variable using a linear model. The most general case is multivariable linear regression in which a

model is created for the relationship between several independent input variables (characteristic variables) and one dependent variable. The model remains linear as the output is a linear combination of the input variables.

In a more general case called polynomial regression the model becomes a non-linear combination of the variables.

The non-linear regression function is characterized by a response variable of nature dichotomous or categorical which can assume two values, of type 1/0, which it identifies healthy (1) and insolvent or anomalous (0) companies. The dependent variables most often used for these models are represented by balance sheet ratios and other financial indicators that describe the economic and financial performance of the company in a given period.

The probability that a company is insolvent or not is therefore conditioned by the realization of its variables, or rather of the economic-financial indicators.

The advantages related to the use of these models are to be found in the speed of modeling, and in cases where the relationship to be modeled is not extremely complex and if amount of data is radar limited. Linear regression is simple to understand and can be very useful .On the other hand, for non-linear data, polynomial regression can be rather difficult to design, since to have information about the data structure and the relationship between the variables of the features is needed. This models aren't as good as others when it comes to highly complex data.

In order to first perform features selection and then predict mortality within 6 months from hospitalization we used the following models:

2.6.4 Least absolute selection and shrinkage operator

One of the innovations introduced in this work is the use of a ML technique to perform a proper selection of the variables of interest that will be part of the composite indicator, eliminating variables considered redundant or irrelevant. It is the Least Absolute Shrinkage and Selection Operator (LASSO), a technique of regularization belonging to the family of embedded methods. In ML, the process of regularization consists of searching for variables through their subspace, introducing additional information to prevent data overfitting. This technique was introduced in 1996 [62]. A fundamental characteristic of LASSO regression concerns the management of less important features: it performs a real selection of independent variables reducing the remaining regression coefficients

to zero and penalizing the regression model with a penalty term L1, the sum of absolute coefficients. There are two types of penalty:

• L1 (absolute size), penalizes the absolute value of the coefficients,

• L2 (squared size) penalizes the square of the coefficients.

It is just the L1 term that has the effect of forcing some coefficients, which are believed to make a smaller contribution to the model, to be exactly zero. LASSO regression uses exactly L1 term.

Therefore, the objective function to minimize is of the type:

$$regularization\ cost = cost + regularization\ penalty$$

and can be written as:

$$\sum_{i=1}^{M}(y_i - \hat{y}_i)^2 = \sum_{i=1}^{M}(y_i - \sum_{j=0}^{p}\beta_j x_{ij})^2 + \lambda\sum_{j=0}^{p}\beta_j^2 \qquad (2.6)$$

where β are the regression coefficients, $\hat{y}i$ are the fitted values and λ represents the tuning parameter which, multiplied by the sum of the absolute values of the β coefficients (excluding the intercept), defines the term penalty. The LASSO regularized version of the estimator will be the solution to:

$$\min_{\alpha,\beta}\sum_{i=1}^{M}(y_i - \hat{y}_i)^2 \ subject\ to\ \|\beta\| \leq t \qquad (2.7)$$

From the formula (2.6), it is clear that λ=0 produces a null model penalty and the same estimate using the ordinary least squares method. On the other hand, if λ assumes high values ($\lambda \to \infty$), a null model will be produced, in the sense that all coefficients will be zero except the intercept, which has been excluded a priori from the model. Thus, the optimal choice of tuning parameters allows to find a balance between bias and variance, a choice that can be made using the cross-validation method. Cross-validation, also called rotation estimation, is a statistical technique used to validate the significance and accuracy with which a predictive model, usually a ML model, will perform in practice. There are two main types of cross-validation: exhaustive cross validation, which in turn is divided into leave-p-out and leave-one-out cross-validation, and non-exhaustive cross-validation, which is divided into k-fold cross-validation, control method and repeated validation of random subsamples. Non-exhaustive cross-validation methods do not calculate all data set splitting modes and are leave-p-out cross-validation approximations. In this analysis a k-fold cross validation was

performed, since it is easy to understand and to implement. Considering that the main purpose of LASSO is to shrink the number of predictors to avoid overfitting and reduce variance in parameter estimates, a third reason is that k-fold cross validation assesses predictive models producing a lower bias than other methods.

2.6.5 Support vector machines

The Support Vector Machines (SVMs) [63], are a set of supervised learning methods that allow the classification of certain patterns. Supervised learning occurs when the user provides a set of data labeled with the class to which it belongs. Thus every learning algorithm needs a training data set S, which consists of N data belonging to C (set of possible classes).

$$S = \{x_n; y_n\} \qquad |n = 1, \ldots, N; \qquad x_n \in R^D \qquad y_n \in C \tag{2.8}$$

(with x_n being a d-dimensional vector, y_n the class of data to which it belongs. The mapping function $y_n = f(x)$ binds to each data element the class whose belonging is not known, therefore the purpose of a supervised learning algorithm is precisely to find this function. Each learning process is divided into two phases:

- training phase (training) in which the algorithm analyzes training data extracted from the entire available data set, to build a model that approximates the mapping function.
- testing phase, in which the created model is tested on a different set of data to evaluate its performance.

2.6.5.1 Nonlinear support vector machines

Many optimization problems cannot be solved using a linear decision function. This occurs when the training data is not separable in the input space R^n. To solve this problem a mapping function φ can be used that is able to map the data in a space of larger size than the input one (Figure 2.27):

$$\phi : R^n \rightarrow \quad R^m \qquad con \quad m > n$$

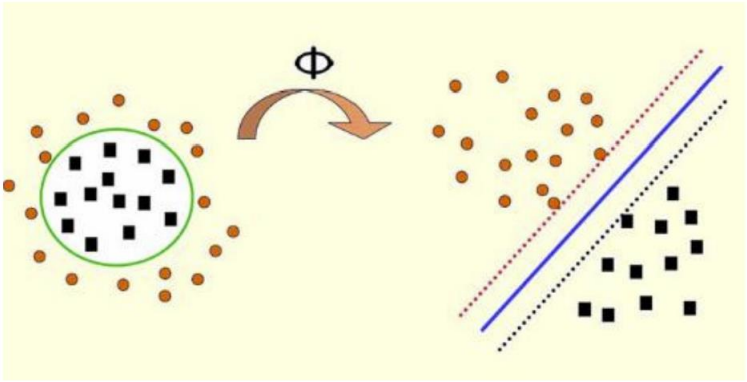

Figure 2.27: mapping through the function φ of non-linearly separable data in a space where they are separable.

In this way the data is linearly separable in the new space. The procedure is identical to that used for linearly separable data using the Lagrangian L_d in which the training data appears as a dot product $\vec{x}_n\vec{x}_i$.

In the new space an optimal linear classifier can always be built replacing the scalar product $\vec{x}_n\vec{x}_i$ with a scalar product $\phi(\vec{x}_n)\phi(\vec{x}_i)$. Therefore the size of the feature space has increased, however this causes calculation problems, because during the training phase the algorithm must work with large vectors. To overcome this drawback, a kernel function [64] which returns the product of images without ever explicitly executing the product between vectors:

$$K(\vec{x}_n, \vec{x}_i) = \phi(\vec{x}_n)\phi(\vec{x}_i) \tag{2.18}$$

By replacing the scalar products of Eq. (2.18) with the kernel function the new decision function is obtained:

$$f(x) = sign(\sum_{n=1}^{N} \alpha_n y_n K(\vec{x}_n, \vec{x}_i) + b) \tag{2.19}$$

Some examples of kernels that can be implemented in nonlinear SVMs are:

- Linear:

$$K(\vec{x}, \vec{y}) = (\vec{x} \cdot \vec{y})$$

- Polynomial of degree p:

$$K(\vec{x}, \vec{y}) = (\vec{x} \cdot \vec{y} + 1)^p$$

- Radial Basis Function (RBF) :

$$K(\vec{x}, \vec{y}) = exp(-\gamma \parallel \vec{x} - \vec{y} \parallel^2)$$

- Gaussian Radial Basis Function :

$$K(\vec{x}, \vec{y}) = exp(-(\vec{x} - \vec{y})^2/2\sigma^2$$

- Multi-Layer Perceptron :

$$K(\vec{x}, \vec{y}) = \tanh(b(\vec{x} \cdot \vec{y})) - c)$$

The kernel function must be chosen very carefully for the type of problem to be solved. It is always possible to transform the input space into a larger one but you have to be careful not to fall into problems of overfitting because the classifier could generalize badly about data never seen. However, there are no theoretical criteria for choosing a type of kernel function and its parameters rather than another; usually needed a check on a validation set.

3 Results

This section presents the results that have been obtained in the project. Paragraph 3.1 describes the structure, functioning and integration of the EHRS, while paragraphs 3.2 and 3.3 describe the results of the two applications of AI models to the real data coming from EHRS.

3.1 An interoperable Electronic Health Record System for clinical cardiology

3.1.1 Description of the CEHRS modules

Both VS and PAM hospital cardiology wards have three main sections, which are: the intensive coronary care unit, in which vital functions are supported and constantly monitored, the post-intensive care unit, for patients who survive critical illness and intensive care, and the day hospital, which patients attend for daily assessment, treatment or rehabilitation.

A global scheme of the presented CEHRS is shown in Figure 3.1 In the following, we report a short explanation for each module in the picture that can be accessed from each of the sections described above.

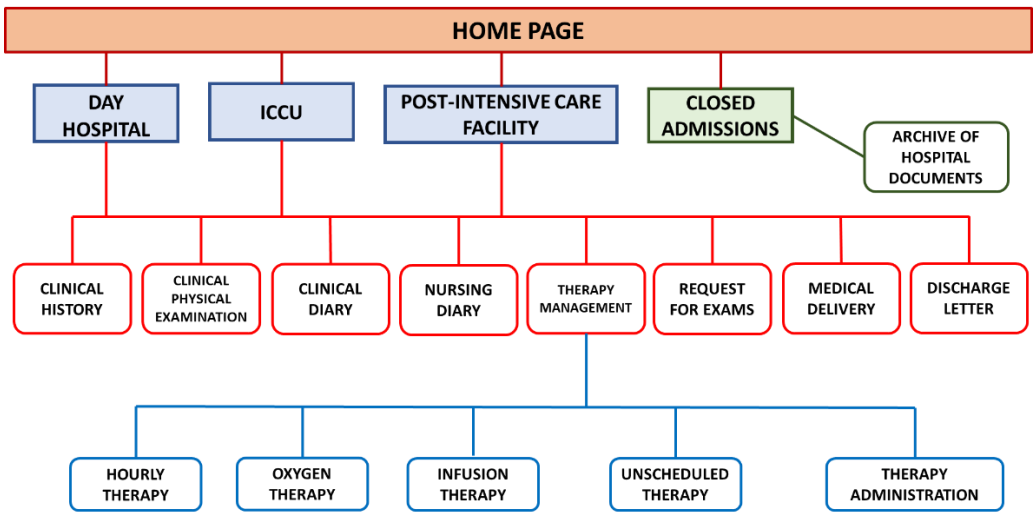

Figure 3.1: Global scheme of the CEHRS

Clinical history. This section has the following four subsections: anamnesis, risk factors, allergies, admission reason. The anamnesis subsection is composed of the past anamnesis, the recent anamnesis and the previous therapy, which are free text fields. The risk factors subsection considers dyslipidaemia, hypertension, familiarity, diabetes, smoke, renal failure and liver failure. A list of possible values is provided for each of these parameters. The allergies subsection relates to drug allergies and to other allergies and intolerances. A predefined list is provided and further information can be included in a free text field. The admission reason subsection summarizes the pathologies that caused the patient's admission, which is very important information for clinical, legal and administrative purposes. This information is included in a free text field. Considering the frequent re-hospitalizations of patients in this type of wards, the system automatically presents the previous content of these sub-sections if available. These contents are modifiable if necessary. For previous admissions it is possible to inherit fields that are not usually changed. This section can be modified by physicians. Nurses have read-only access rights.

Physical examination. This section contains the diagnostic plans that are carried out in order to ascertain the presence or absence of deviations from the physiological normality condition of the patient. It is divided into categories according to the body district (general, abdomen, cardiovascular system etc.). Each category contains a list of parameters with predefined values, and it is possible to add free text to describe cases apart from the list of parameters. A multiple choice and binary choice question structure has been adopted. This choice supports standardization, but it requires a compromise between completeness and effective visualization. This section can be modified by physicians. Nurses have read-only access rights.

Therapy management. This section has the following five subsections: the hourly therapy, the oxygen therapy, the infusion therapy, the unscheduled therapy and the therapy administration. The hourly therapy scheme requires in the first place the identification of the prescribed drug by its commercial name, weight, active ingredient and pharmaceutical form. The insertion of the name of the drug is supported by a completion tool that draws from the list of drugs provided by the Liguria region. The identification is based on the Italian pharmaceutical identification system (AIC), according to the RHII rules. The therapy administration class diagram is shown in Figure 3.2.

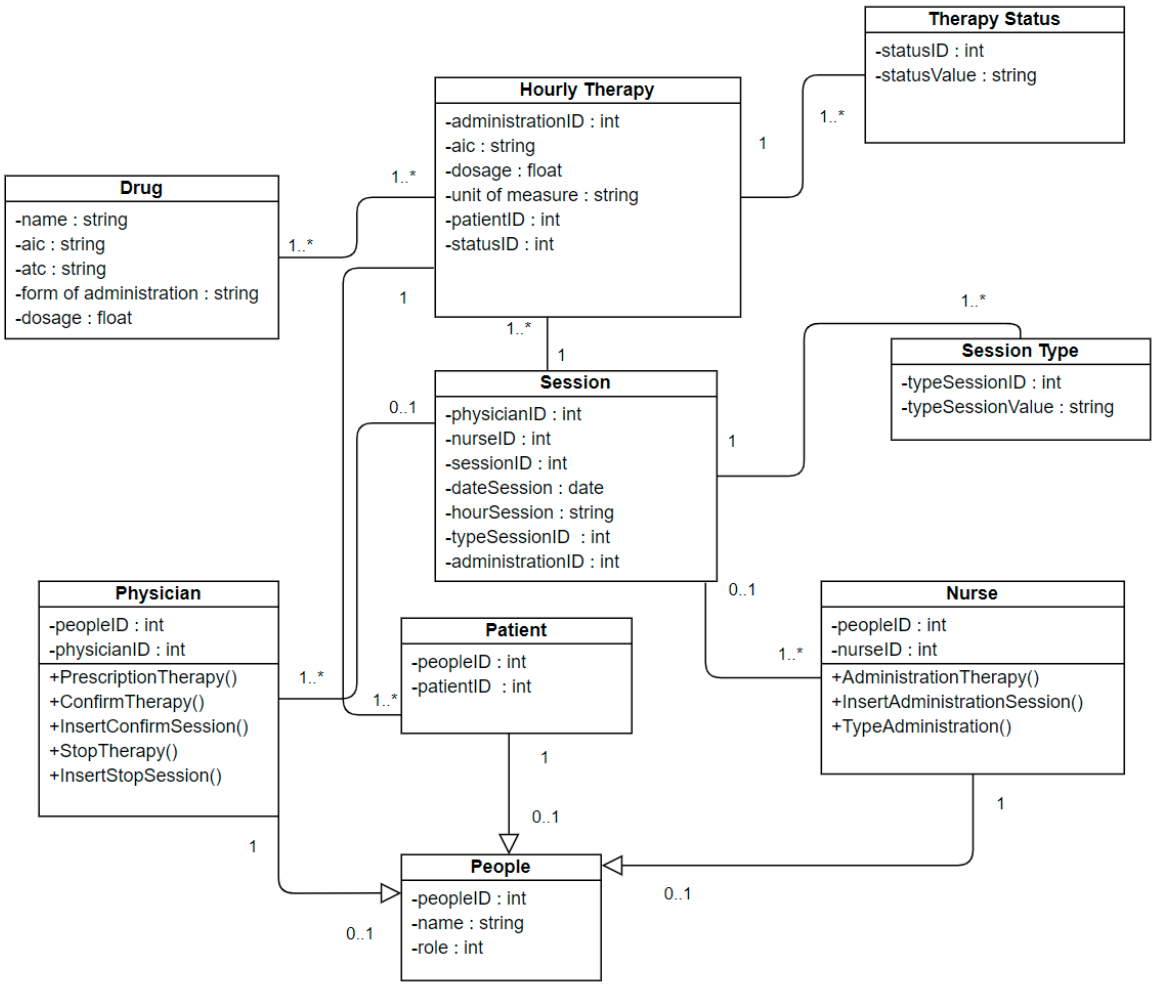

Figure 3.2: Therapy administration class diagram.

The oxygen therapy subsection allows the physician to choose the operating modes and the related parameters. A prescription support procedure has been set up with a set of predefined prescription set-ups parametrized to patient data (such as weight and body mass index). The infusion therapy subsection shows the combinations of suitable drugs. When the combination is chosen, the physician can choose some parameters. The other parameters are calculated according to the guidelines. In the three subsections above, some tools are available to support fast prescription repetition, with explicit confirmation for each day. In the unscheduled therapy subsection, a fast drag search tool is available for one-time prescriptions. In all these prescription subsections, nurses have read-only access rights. The last subsection is devoted to drug administration. This subsection contains tools for fast and safe therapy identification and for the annotation of drug administration related events. In this section, physicians have read-only access rights.

Clinical diary. In this section, physicians and nurses can describe significant events by free text. When questioned, this section shows the author of each annotation, the changes and the compilation timing. Nurses have read-only access rights.

Nursing diary. This section is similar to the clinical diary section, but it relates to the nursing treatment. Physicians have read-only access rights.

Requests for exams. This section contains an order entry tool for physical examinations and a communication tool to exchange physical examination related information among staff. This section can be modified by physicians. Nurses have read-only access rights.

Medical deliveries. This section is similar to the clinical diary section, but it is less structured and contains information for physicians that take over in hospital shifts. The information is recorded as free text.

Hospital discharge letter (HDLET). This section allows the physician to write the discharge letter as a collection of required and optional fields. These fields are free text, but specific algorithms described in the following sections have been implemented to support hospital discharge letter drafting.

Closed hospital admissions. This section allows the user to perform searches within the admission lists in which the patients have been discharged or are dead. The physician can view all the data related to the required hospitalization. This option is useful for new hospitalizations of the same patient or other similar cases.

3.1.2 Interoperability tools

As mentioned in the Materials and Methods section, one of the main aims of the hospital management was to obtain interoperability of CEHRS with the other tools in the HIS. All main interfaces of the CEHRS are shown in Figure 3.3.

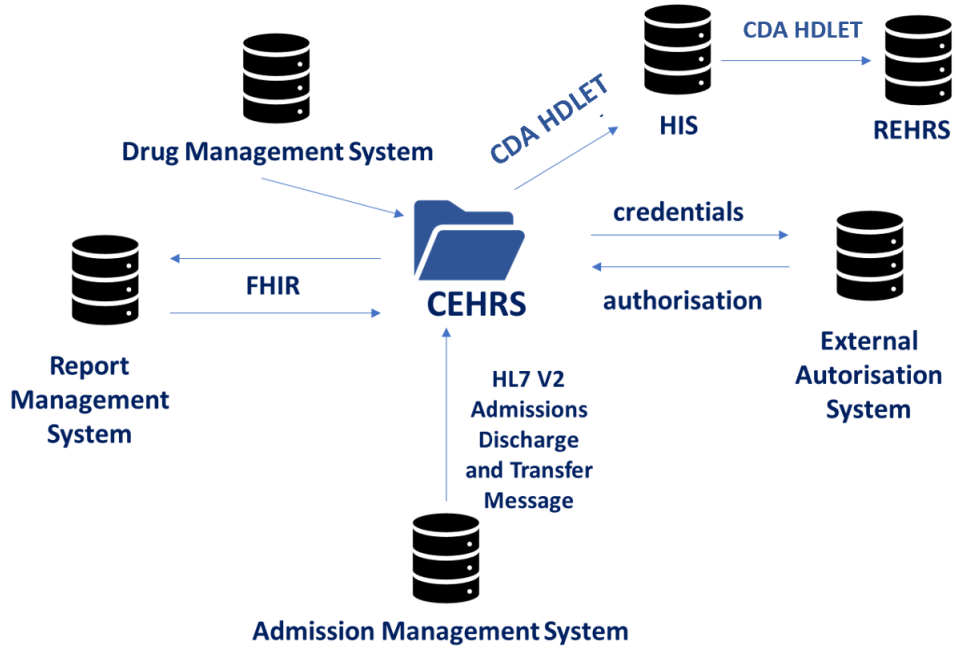

Figure 3.3: CEHRS Interfaces with other components of the HIS

3.1.2.1 Authentication and authorization procedure

The CEHRS has been designed according to the role base access control principles. The access and role attribution are controlled by an external authorization system (EAS), developed according to the Lightweight Directory Access Protocol (LDAP). The CEHRS exchanges credentials and authorization certificates with EAS with strict temporary limits to avoid unauthorized access.

3.1.2.2 Admission management system

Both hospitals share a general-purpose software for the management of patient ADT events. This software points out the occurrence of each ADT event by an HL7 V2 ADT Message. The CEHRS includes a web service that receives such messages, interprets them and, if the event involves the cardiologic ward, changes the internal patient list according to the ADT message (Figures 3.4 and 3.5).

Figure 3.4. Admission system by HL7 V2 ADT messages

```
MSH|^~\&|SIVIS||||20161207173711.0000+0100||ADT^A01|1481128631587|P|2.5
EVN|A01|20161207173711.773+0100
PID|||PRVTVL00A01D969T^^^^CF~1742319^^^^PIN||ITSVIL^PROVA||20000101
000000.0000+0100|M|||^^^^^010025^N^^~VIA CASTELLUCCIO
001400^^^^^010025^L||^^^^^^010000030434||||||||||||100
PV1|1|I|0801^^^^^^^^UTIC POST
INTENSIVA|||||||||||||||08012016708573|||||||||||||||||||||20160628212400
```

Figure 3.5. ADT message used in the integration shown in Figure 4 (SIVIS—mentioned in the message—is the local name for HIS).

3.1.2.3 Report management system

Both hospitals and other health care facilities in Genoa share a PACS/RIS to store images, signals and diagnostic reports. The CEHRS has to interface with this PACS/RIS to ensure this information is available on the ward. This interface has been developed within this project according to RLUS specifications [65].

Two temporal interface sequences are described in the following section.

The first sequence is organized as follows (Figure 3.6).

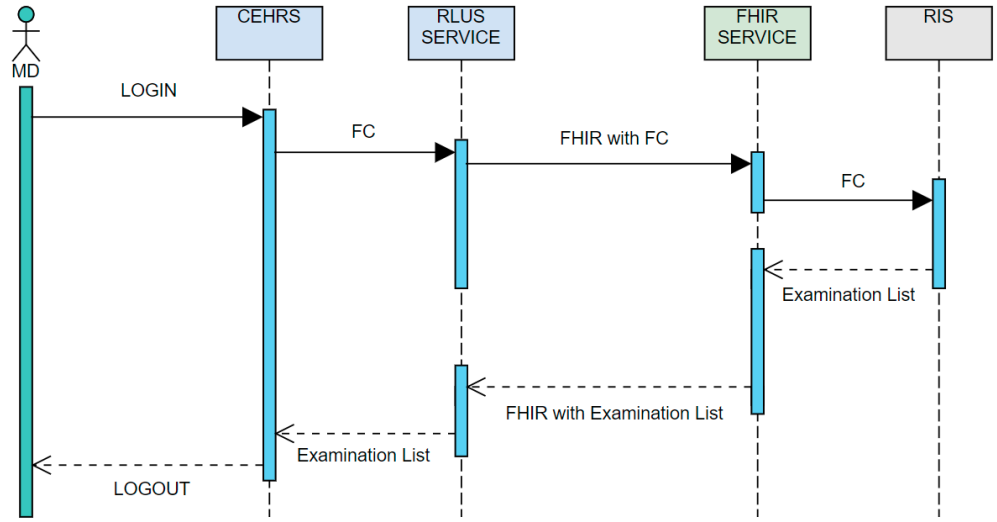

Figure 3.6: Pathway for search and retrieval of the diagnostic report list.

- The user chooses the patient whose reports he/she wants to visualize. This is the “trigger event”, which is used by the HL7 environment to start the process that re-trieves the requested information.
- The fiscal code (FC) of the patient is transmitted to the RLUS service by a FHIR message (FC is used in Italy as a unique identifier of Italian citizens; in this context, only communications protected by the HIS firewall are allowed to use FCs). The RIS provides the list of all available reports for each patient to the RLUS service by a FHIR message and the RLUS sends the list of exams to the CEHRS.

The HL7 message for the retrieval of the FC through RLUS is shown in Figure 3.7. The interface looks for the diagnostic report list using a “search by criteria” procedure that is set to a filter where the Boolean expression is the comparison of all available FCs with the selected FC.

```
<soapenv:Body>
  <rlus:ListRLUSGenericRequest>
      <rlus1:RLUSSearchStruct semantic-signifiername="DiagnosticReport">
        <rlus1:searchByCriteria>
          <rlus1:FilterCriteria>
            <rlus1:Expression>
              <exp:BinaryTerm  text="#subjectIdentifierSystem" type="Text"/>
              <exp:Operator type="EqualTo"/>
              <exp:BinaryTerm text="2.16.840.1.113883.2.9.4.3.2" type="Text"/>
            </rlus1:Expression>
            <rlus1:Expression>
              <exp:BinaryTerm text="#subjectIdentifierValue" type="Text"/>
              <exp:Operator type="EqualTo"/>
              <exp:BinaryTerm text="CTTNVO04R10F205J" type="Text"/>
            </rlus1:Expression>
          </rlus1:FilterCriteria>
          <rlus1:OrderCriteria>
              <rlus1:Order name="#effectiveDateTime" direction="DESC"/>
              </rlus1:OrderCriteria>
        </rlus1:searchByCriteria>
        <rlus1:searchByExample>FILTERED SEARCH</rlus1:searchByExample>
      </rlus1:RLUSSearchStruct>
  </rlus:ListRLUSGenericRequest>
</soapenv:Body>
```

Figure 3.7. RLUS message for the transfer of the FC.

The second temporal sequence is organized as follows (Figure 3.8).

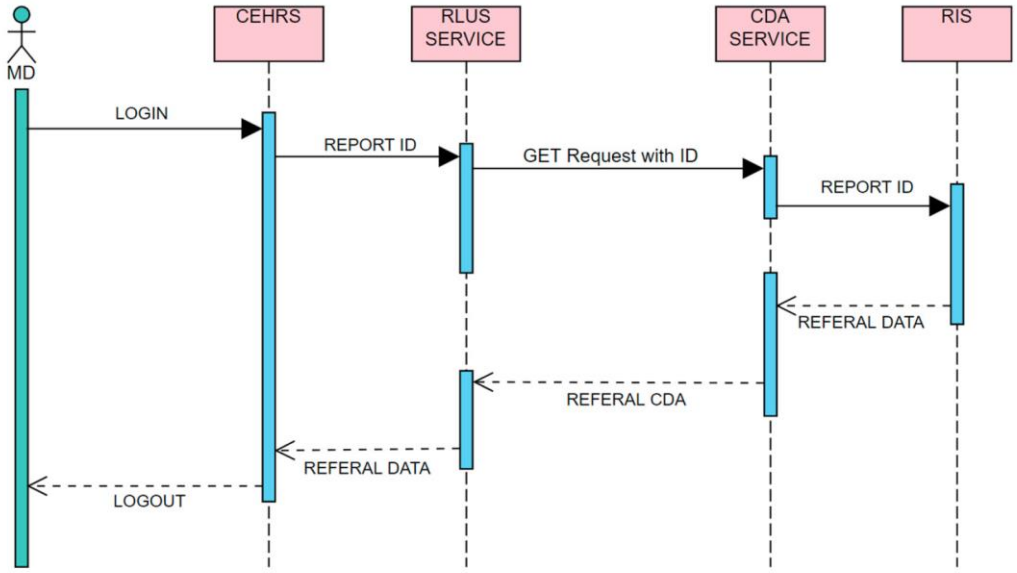

Figure 3.8: Pathway for the retrieval of a diagnostic report.

- The user chooses the report he/she requires.
- The metadata of the report are transferred to the RIS by the RLUS service, and subsequently by the CDA service, which finds the report and sends it to the CEHRS.

CDA is formatted according to the Italian Implementation Guide for diagnostic re-ports.

3.1.2.4 HDLET management system

When a patient is discharged, the hospital must produce an HDLET, that is, the main document, summarizing the events during the hospitalization and providing indications for the treatment of the patient in the follow-up. The HDLET must be stored in the HIS and also sent to the regional EHRS as the CDA.

The CEHRS enables physicians to write the HDLETs starting from all the relevant in-formation, collected in a semi-automatic way. When the HDLET is completed, CEHRS implements the CDA (according to the Italian Implementation Guide for HDLET), communicates with the digital signature system to produce a HDLET signed CDA and sends it the RLUS, which splits it into fields that are included in the HIS. The signed CDA is also sent to the REHRS to ensure it is available for the patient's follow up (Figure 3.9).

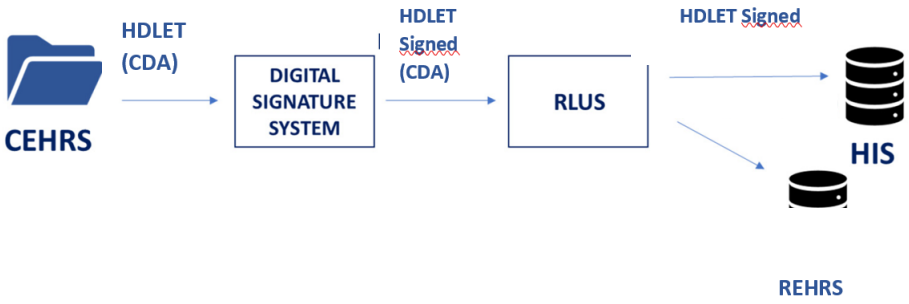

Figure 3.9: Pathway for the delivery of the HDLET.

3.1.2.5 Implementation of the CDA of the HDLET

The Web Service must allow standardized export of medical record data cardiology, contained in the Database.

The implementation of the web service was carried out on the integrated development environment Microsoft Visual Studio 2019 and was developed using Visual Basic as a language programming and the WCF Service. The WCF adopted in this implementation contains:

- a file with the extension .svc, Service.svc, which represents the actual service.
- an IService.vb file, which represents the service interface; it contains all the signatures of the public methods and classes exposed by the web service.
- a Service.vb file, where the methods declared in the IService.vb file are implemented.
- a vb file, where the translated classes for the CDA are located.
- a Web.config file, where configuration information is contained.

When creating the WCF, IService.vb and Service.vb, the Web.config and the Service.svc were automatically generated. Instead, the vb file was created by me and, therefore, subsequently introduced within the project. This file, which contains the translation of the standard CDA classes with the respective variables and property, was included within the WCF since the latter was structured on the basis of the HL7 CDA R2 standard. XSD were used to create this file, provided by HL7 V3 and as a translation tool the Microsoft software xsd.exe and, therefore, the classes thus obtained reflect exactly the same structure of the elements defined in the HL7 V3 standard. XSD is a particular language designed to describe the structure and content of XML documents, which has obtained the official validation of the WCF. An XSD defines the type of an XML document in terms of constraints: which elements and attributes can appear, in what relationship to each other, what type

of data it can contain e other. HL7 provides several XSD files for the CDA connected by an inheritance mechanism.

Therefore, the translation of the main .xsd file (POCD_MT000040.xsd) allowed to obtain the translation of the entire HL7 CDA into a file written in Visual Basic (VB) programming language in order to take advantage of the classes and attributes defined in the models during standardized export of data from the Web Service. The XML Schema Definition tool (Xsd.exe) is installed in the .NET tools Framework as a Windows Software Development Kit tool and allows you to generate Common Language Runtime or XML Schema classes from XDR, XML, and XSD files or from classes of a runtime assembly. In this project the XML Schema Definition tool was used to translate the XSD in VB classes and, therefore, to generate runtime classes from an XSD schema file.

In the following some examples of CDA classes translated into VB are presented. The specific details of definitions of foundational CDA classes (CE, CS,….) can be find in the HL7 CDA model[66].

These classes can be used with XmlSerializer to read and write XML code based on the scheme. So to get a good translation of the CDA, the POCD_MT000040.xsd file was manually edited. This change has been made in all the files that have been translated. The purpose of these changes is to create a new complex type, using the <xs: complexType> element. Before each line in which the declaration <xs: complexType>, I inserted the element <xs: element name = "and _..." type = ”...”>, specifying the name of the complexType considered. For example, first of the element <xs: complexType name = "POCD_MT000040.ClinicalDocument">, the declaration <xs: element name = "e_POCD_MT000040.ClinicalDocument" type = "POCD_MT000040.ClinicalDocument" /> (Figure 3.10) was inserted.

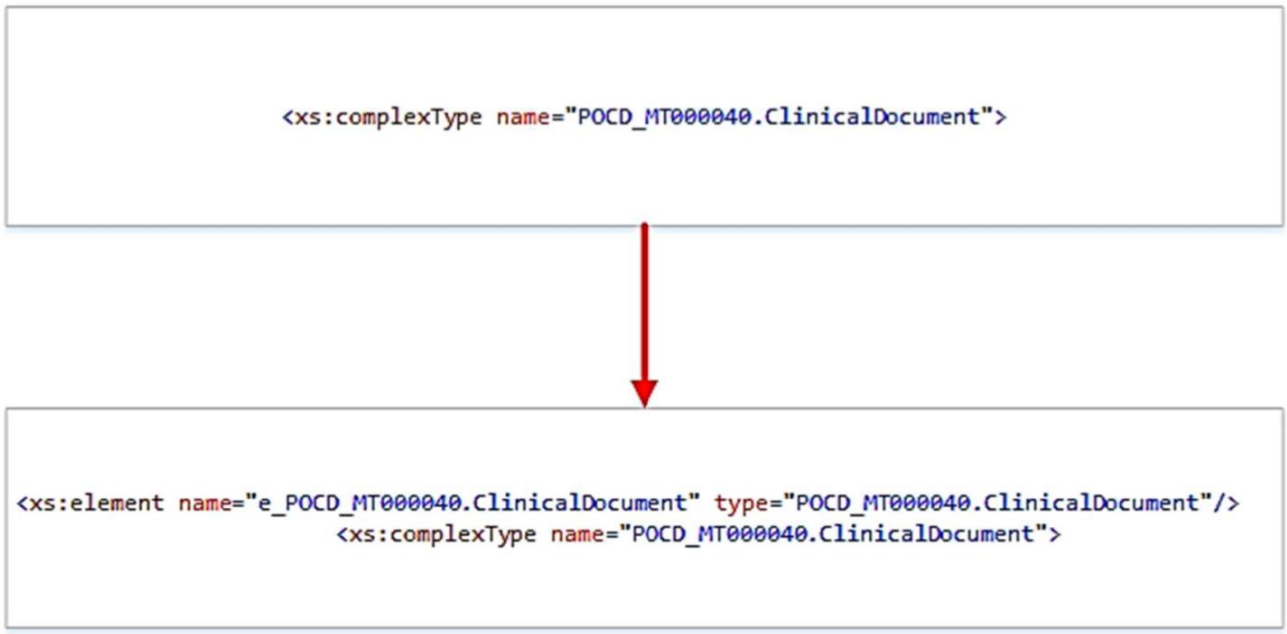

Figure 3.10: Example of the changes made

After making these changes to the POCD_MT000040.xsd file, I started the Prompt commands for developers for VS2016 and using the appropriate commands I created a POCD_MT000040.vb file. The created POCD_MT000040.vb file is, therefore, the translation into classes of the HL7 CDA, written with the Visual Basic programming language.

This file has been inserted into the WCF, in order to call the classes to form the Board of Directors. The classes reflect exactly the same structure as the defined elements in the HL7 v3 standard. Each one has its own constructor, characteristic variables, and related properties (Figure 3.11).

```
1.  Partial Public Class POCD_MT000040ClinicalDocument
2.
3.      Private realmCodeField() As CS
4.
5.      Private typeIdField As POCD_MT000040InfrastructureRoottypeId
6.
7.      Private templateIdField() As II
8.
9.      Private idField As II
10.
11.     Private codeField As CE
12.
13.     Private titleField As ST
14.
15.     Private effectiveTimeField As TS
16.
17.     Private confidentialityCodeField As CE
18.
19.     Private languageCodeField As CS
20.
21.     Private setIdField As II
22.
23.     Private versionNumberField As INT
24.
25.     Private copyTimeField As TS
```

```
26.
27.     Private recordTargetField() As POCD_MT000040RecordTarget
28.
29.     Private authorField() As POCD_MT000040Author
30.
31.     Private dataEntererField As POCD_MT000040DataEnterer
32.
33.     Private informantField() As POCD_MT000040Informant12
34.
35.     Private custodianField As POCD_MT000040Custodian
36.
37.     Private informationRecipientField() As POCD_MT000040InformationRecipient
38.
39.     Private legalAuthenticatorField As POCD_MT000040LegalAuthenticator
40.
41.     Private authenticatorField() As POCD_MT000040Authenticator
42.
43.     Private participantField() As POCD_MT000040Participant1
44.
45.     Private inFulfillmentOfField() As POCD_MT000040InFulfillmentOf
46.
47.     Private documentationOfField() As POCD_MT000040DocumentationOf
48.
49.     Private relatedDocumentField() As POCD_MT000040RelatedDocument
50.
51.     Private authorizationField() As POCD_MT000040Authorization
52.
53.     Private componentOfField As POCD_MT000040Component1
54.
55.     Private componentField As POCD_MT000040Component2
56.
57.     Private nullFlavorField As String
58.
59.     Private classCodeField As ActClinicalDocument
60.
61.     Private classCodeFieldSpecified As Boolean
62.
63.     Private moodCodeField As String
```

Figure 3.11: Class POCD_MT000040ClinicalDocument

The POCD_MT000040ClinicalDocument class was used to define the type of the function that creates the CDA to send to the Client.

```
<ServiceContract()>
Public Interface IService

    <OperationContract()>
    Sub Crea_CDAXML(ByVal Id_Ricovero As String, ByVal Id_Paziente As String, By
                                                          Ref errstr As String)
End Interface
```

Figure 3.12: Create_CDAXML () function

The messages sent are described through operation contracts in the interface of service. The WCF exposes only the Iservice.vb interface which only declares the Create_CDAXML () function. The actual implementation of the functions is done in Service.vb and is unknown to the client. The Iservice.vb defines the operation by creating the Create_CDAXML () method and marking it with the OperationContract () attribute. So to create a service, the operation is declared within an interface marked with the ServiceContract () attribute. The Create_CDAXML () function, therefore, is the one that is called by the Client [Figure 3.12].

```
Private Sub LDO_Load(sender As Object, e As EventArgs) Handles Me.Load
    Dim id_paz As Integer = CInt(Request.QueryString("id_p"))
    Dim id_ricov As Integer = CInt(Request.QueryString("id_ric"))
    Dim cliente As New ServiceReference3.ServiceClient
    cliente.Crea_CDAXML(id_ricov, id_paz, lbl_errore2.Text)
End Sub
```

Figure 3.13: Detail of the implementation

After the request made by the Client, via the HTTP transport protocol, the Web Service will respond by creating a new CDA in XML format with the information requests for hospital discharge letter, generated with the function Create_CDAXML (), which in turn calls the Create_CDA () function which implements the classes of the POCD_MT000040.

```
Public Sub Crea_CDAXML(ByVal Id_Ricovero As String, ByVal Id_Paziente As String,ByRef
                                errstr As String) Implements IService.Crea_CDAXML
        Dim int As Integer = 0
        Dim CDA As POCD_MT000040ClinicalDocument
        CDA = Crea_CDA(Id_Ricovero, Id_Paziente, errstr)
 Dim ser As XmlSerializer = New XmlSerializer(GetType(POCD_MT000040ClinicalDocument))
Dim xml As XmlWriter = XmlWriter.Create("C:\Users\carlamelis91\Desktop\TESI\Farmaciok
\cda_ldo" & "\" & "LDO_"& Id_Ricovero & ".xml")
        xml.Close()
  Dim path As String = "C:\Users\carlamelis91\Desktop\TESI\Farmaciok\cda_ldo" & "\" &
 "LDO_" & Id_Ricovero & ".xml"
        Dim writer As TextWriter = New StreamWriter(path)
        ser.Serialize(writer, CDA)
        writer.Close()


   End Function
```

As previously mentioned, a CDA document consists of a Header and a Body. In this paragraph, the description and the its implementation in the Create_CDA () function is shown:

Public Function Crea_CDA(ByVal Id_Ricovero As String, ByVal Id_Paziente As String, By Ref errstr As String) As POCD_MT000040ClinicalDocument

3.1.2.5.1 CDA header of the HDLET document

In the header of the Board of Directors, as already mentioned, all management information is shown of the document, such as, for example, date and time of issue, the patient to whom it refers, the author doctor, etc.

3.1.2.5.1.1 Document Root: <ClinicalDocument>

Every CDA document must start with this element, which includes **xsi**: **schemaLocation**, **xmlns** and **xmlsn**: **xsi** as special attributes, which specify the reference to a external namespace:

```
<ClinicalDocument xsi:schemaLocation="urn:hl7-org:v3 CDA.xsd"
xmlns="urn:hl7-org:v3"
xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance">
```

3.1.2.5.1.2 Domain: <realmCode>

It is a mandatory element that indicates the domain to which the document belongs.

Attribute	Type	Values	Details
code	CE	“IT”	Defines the id of context for Italy.

In the translation into classes of VB realmCode is of type CS (as we can see from the figure above), its implementation is therefore:

```
Dim Header_realmCode(0) As CS
Dim realmCode As New CS
realmCode.code = "IT"
Header_realmCode(0) = realmCode
```

3.1.2.5.1.3 Identification of the CDA2: <typeId>

It is a mandatory element that indicates that the document has been structured according to specifications HL7-CDA Rel 2.0. Represents a unique identifier.

Attribute	Type	Values	Details
root	OID	“2.16.840.1.113883.1.3”	HL7 OID for registered models
extension	ST	“POCD_HD000040”	Identification encoding of the "CDARelease Two Hierarchical Description" which is the schema that contains the class hierarchy of a CDA document.

In the case of translation into classes typeId is defined as POCD_MT000040InfrastructureRoottypeId, which we can define as:

```
Partial Public Class POCD_MT000040InfrastructureRoottypeId
    Inherits II
End Class

Partial Public Class II
    Inherits ANY

    Private rootField As String

    Private extensionField As String

    Private assigningAuthorityNameField As String

    Private displayableField As Boolean

    Private displayableFieldSpecified As Boolean
```

So the implementation is:

```
Dim Header_TypeId As New POCD_MT000040InfrastructureRoottypeId
Header_TypeId.root = "2.16.840.1.113883.1.3"
Header_TypeId.extension = "POCD_HD000040"
```

3.1.2.5.1.4 HL7 template identifier: <templateId>

Indicates the reference template for the CDA document. It is made up of the attributes:

Attribute	Type	Value	Details
root	OID	"2.16.840.1.113883.2.9.10.1.5"	Root of the Discharge Letter template for Hl7 Italy.
extension	ST	Template version. Not valued in the first version	Identifier of the Template described in present document.

In this case the implementation is:

```
Dim Header_template_id As New II
Header_template_id.root = "2.16.840.1.113883.2.9.10.1.5"
Dim H_templ(0) As II
H_templ(0) = Header_template_id
```

3.1.2.5.1.5 Identification of the document: <id>

This element uniquely identifies the instance of each CDA document. It is a value of the type HL7 "Instance Identifier" and is composed of the following attributes:

Attribute	Type	Value	Details
root	OID	[OID IDENTIFICATION OF THE COMPETENCE STRUCTURE]	Unique identifier of the domain identification of documents (ad e.g. can indicate the ASL of competence of the document or the hospital ward of the ASL/AO). This identifier – recognized publicly – guarantees uniqueness of the instance of the unique document identifier.
extension	ST	[IUD]	Generated by the author's client according to shared rules, so to avoid collisions within the same domain of competence (e.g. ASL/AO/Region of competence).

assigningAuthorityName	ST	[NAME COMPETENCE STRUCTURE]	Identification domain name of documents (eg.ASL/AO/Region of competence).

In this case, the implementation is:

```
Dim Header_Id_CDA As New II
Header_Id_CDA.extension = "LDO_" & Id_Ricovero
Header_Id_CDA.root = "OID ASL 3 villa scassi"
Header_Id_CDA.assigningAuthorityName = "ASL 3 VILLA SCASSI"
```

3.1.2.5.1.6 Document code: <code>

It reports a code that identifies the type of document to which the Board of Directors refers, this value must refer to the LOINC coding system.

Attribute	Type	Value	Details
codeSystem	OID	“2.16.840.1.113883.6.1"	OID of the code encoding system LOINC document

The code element is of type CE in the classes in VB:

```
Partial Public Class CE
    Inherits CD
End Class

Partial Public Class CD
    Inherits ANY

    Private originalTextField As ED

    Private qualifierField() As CR

    Private translationField() As CD

    Private codeField As String

    Private codeSystemField As String

    Private codeSystemNameField As String

    Private codeSystemVersionField As String

    Private displayNameField As String
```

In this case, the implementation is:

```
Dim Header_Code As New CE
Header_Code.code = "34105-7"
Header_Code.codeSystem = "2.16.840.1.113883.6.1"
Header_Code.codeSystemName = "LOINC"
Header_Code.codeSystemVersion = "2.19"
Header_Code.displayName = "Lettera di dimissione ospedaliera"
```

3.1.2.5.1.7 Document creation date: <effectiveTime>

Indicates the creation date of the CDA document. It consists of the following attribute:

Attribute	Type	Value	Dettails
			Year, month, day, hour, minutes, seconds. The hours must be reported in the interval 00:00:00 - 23:59:59. ZZZZ represents the offset

value	TS	[YYYYMMDDHHMMSS+|-ZZZZ]	than the time of Greenwich (GMT - Greenwich Mean Time). The offset value it will depend on daylight saving time settings; for Italy it may vary between ZZZZ enhanced with +0100 or +0200 (in case of summer time)

The Implementation is follows:

```
Dim Header_EffectiveTime As New TS
Dim data_o As DateTimeOffset = Now

Dim data As String = data_o.ToString
Dim data_split(3) As String
data_split = Split(data, " ")
Dim ggmmaa As String = data_split(0)
Dim orario As String = data_split(1)
Dim offset As String = data_split(2)
Dim data_giorni_split(3) As String
data_giorni_split = Split(ggmmaa, "/")
Dim giorno As String = data_giorni_split(0)
Dim mese As String = data_giorni_split(1)
Dim anno As String = data_giorni_split(2)
Dim ora_split(3) As String
ora_split = Split(orario, ".")
Dim ora As String = ora_split(0)
Dim min As String = ora_split(1)
Dim sec As String = ora_split(2)
Dim off_split(2) As String
off_split = Split(offset, ":")
Dim off1 As String = off_split(0)
Dim off2 As String = off_split(1)
```

```
Dim data_compl As String = anno & mese & giorno & ora & min & sec & off1 & off2

Header_EffectiveTime.value = data_compl.ToString
```

3.1.2.5.1.8 Confidentiality of the document: <confidentialityCode>

Specifies the level of confidentiality of the document, reports a code that identifies the level of confidentiality of the CDA document according to the code of "Confidentiality" of HL7 defined as Normal, Restricted, Very restricted. In this specific case, the element must be valued as:

Attribute	Type	Value	Details
codeSystem	OID	“2.16.840.1.113883.5.25"	OID encoding.
code	ST	"N", "R", "V"	Rules of confidentiality
codeSystemName	ST	"Confidentiality"	Name of the coding.

CE is the same type found for the document code, so the implementation is follows:

```
Dim Header_ConfidentialityCode As New CE
Header_ConfidentialityCode.code = "N"
Header_ConfidentialityCode.codeSystem = "2.16.840.1.113883.5.25"
Header_ConfidentialityCode.codeSystemName = "Confidentiality"
Header_ConfidentialityCode.displayName = "Normale"
```

3.1.2.5.1.9 Language and domain: <languageCode>

It indicates the language in which the document is drawn up and in the case of the HDLET how it must be completed:

Attribute	Type	Value	Details
code	ST	“it-IT”	Identification of the name of then language

Translated into VB classes this element is of type CS:

```
Partial Public Class CS
    Inherits CV
End Class
Partial Public Class CV
    Inherits CE
End Class
Partial Public Class CE
    Inherits CD
End Class

Partial Public Class CD
```

```
    Inherits ANY

    Private originalTextField As ED

    Private qualifierField() As CR

    Private translationField() As CD

    Private codeField As String

    Private codeSystemField As String

    Private codeSystemNameField As String

    Private codeSystemVersionField As String

    Private displayNameField As String
```

This Implementation is:

```
Dim Header_LanguageCode As New CS
Header_LanguageCode.code = "it-IT
```

3.1.2.5.1.10 Document version: <seltId> and <versionNumber>

They are mandatory elements of which the first maintains a constant value among the different ones versions of the same document, while the second changes as the revision changes. The <seltId> element consists of the following attributes:

Attribute	Type	Value	Dettails
root	OID	[DOCUMENT IDENTIFICATION DOMAIN OID]	Unique identifier of the domain of identification of documents. This identifier - publicly recognized - guarantees the uniqueness of the instance of the identifier a global level.

extension	ST	[IURD]	Unique Identification of the Revision of the document within the domain of identification.

			Generated by the client of the second author rules shared within the domain of competence (defined by the root) in such a way as to ensure the uniqueness of this attribute within the same domain.
assigningAuthorityName	ST	[DOMAIN NAME DOCUMENT IDENTIFICATION]	Domain name of identification of documents.

<versionNumber> consists of the following attributes

Attribute	Type	Value	Dettails
value	INT	[DOCUMENT VERSION]	With each subsequent version of the document, this number must be increased by one unit.

In the case of the first element, the class in VB is associated with a type II that has already been seen previously, the implementation results:

```
Dim Heder_SetId As New II
Heder_SetId.root = "OID DOMINIO IDENTIFICAZIONE DOCUMENTI"
Heder_SetId.extension = "Id_Ricovero"
Heder_SetId.assigningAuthorityName = " NOME DOMINIO IDENTIFICAZIONE DOCUMENTI"
```

In the second case it was decided that the HDLET relates the single document including all its parts, and therefore it cannot have multiple versions (there cannot be multiple versions of the same HDLET). According to this, the mandatory versionNumber element has been set to 1 as follows:

```
Dim Header_versionNumber As New INT
Header_versionNumber.value = 1
```

3.1.2.5.1.11 Patient of the letter: <recordTarget>

It Identifies the patient which is being discharged. It is an element composed of a role <patientRole> performed by a <patient> entity.

3.1.2.5.1.11.1 Patient subject to admission <patientRole>

This element must have at least one element of type <id> that represents the patient's identification key, according to the schemes assigned by each single organization, and possibly further elements of type <id> for information related other identifying elements. The implementation of this section has involved difficulties since there are several possible cases and several exceptions, which they depend on the type of subject in question; such cases may be like this summarized:

- Subjects Insured by foreign institutions;
- Europeans Not Registered (ENI) to the SSN;
- Temporarily Present Foreigners (STP);
- Italian citizen or resident foreigner (registered with the SSN).

Each of these fields has different features and different types of identifiers, which it is not always possible to obtain from the personal information present in the data provided by the Villa Scassi hospital. Many of these fields are not considered and are not included, but are mandatory in the HDLET, only citizens who are registered with the SSN and therefore have the code are considered. Two elements of type <id> are provided for Italian or foreign resident citizens containing:

- The fiscal code of the patient (which is mandatory);
- The code assigned by the regional registry (which is optional).

Since the code assigned by the regional registry is not available, only the first element of type <id>, consisting of the following attributes is considered:

Attribute	Type	Value	Details
Root	OID	"2.16.840.1.113883.2.9.4.3.2"	OID of Ministry of the Economy and Finance.

Extension	ST	[CODICE FISCALE]	Fiscal code of the patient.
AssigningAutorityName	ST	Ministry of the Economy and Finance	Ministry of the Economy and Finance.

The classes relating to the recordTarget element and the element PatientRole just mentioned are shown below:

```
Partial Public Class POCD_MT000040RecordTarget
    Private realmCodeField() As CS
    Private typeIdField As POCD_MT000040InfrastructureRoottypeId
    Private templateIdField() As II
    Private patientRoleField As POCD_MT000040PatientRole
    Private nullFlavorField As String
    Private typeCodeField As String
    Private contextControlCodeField As String
Partial Public Class POCD_MT000040PatientRole
    Private realmCodeField() As CS
    Private typeIdField As POCD_MT000040InfrastructureRoottypeId
    Private templateIdField() As II
    Private idField() As II
    Private addrField() As AD
    Private telecomField() As TEL
    Private patientField As POCD_MT000040Patient
    Private providerOrganizationField As POCD_MT000040Organization
    Private nullFlavorField As String
    Private classCodeField As String
```

Within patientRole the <patient> entity is found, which contains the personal data relating to the patient, whose class, and the classes related to it, are:

```
Partial Public Class POCD_MT000040Patient

    Private realmCodeField() As CS

    Private typeIdField As POCD_MT000040InfrastructureRoottypeId

    Private templateIdField() As II

    Private idField As II

    Private nameField() As PN

    Private administrativeGenderCodeField As CE

    Private birthTimeField As TS

    Private maritalStatusCodeField As CE

    Private religiousAffiliationCodeField As CE

    Private raceCodeField As CE

    Private ethnicGroupCodeField As CE

    Private guardianField() As POCD_MT000040Guardian

    Private birthplaceField As POCD_MT000040Birthplace

    Private languageCommunicationField() As POCD_MT000040LanguageCommunication

    Private nullFlavorField As String

    Private classCodeField As String

    Private determinerCodeField As String
```

```
Partial Public Class PN
    Inherits EN
End Class


Partial Public Class EN
    Inherits ANY

    Private itemsField() As ENXP

    Private validTimeField As IVL_TS

    Private textField() As String

    Private useField() As String


Partial Public Class engiven
    Inherits ENXP
End Class


Partial Public Class enfamily
    Inherits ENXP
End Class
```

The patient section of the letter has been implemented with a function, which takes the data directly from the database:

```vb
Dim Header_RecordTarget(0) As POCD_MT000040RecordTarget
Header_RecordTarget(0) = Crea_Header_RecordTarget(Id_Paziente, errstr)


Public Function Crea_Header_RecordTarget(ByVal Id_Paziente As String, ByRef errstr As
 String)                                                                          As
 POCD_MT000040RecordTarget
       Dim header_Id_Pers As New II
       header_Id_Pers.root = "2.16.840.1.113883.2.9.4.3.2"
       Dim cf As DataTable = funz.dati_paziente(Id_Paziente, errstr)
       If cf.Rows.Count > 0 Then
           header_Id_Pers.extension = cf.Rows(0).Item("CF").ToString
       End If
       header_Id_Pers.assigningAuthorityName = "Ministero Economia e Finanze"

       Dim header_Id_Persona(0) As II
       header_Id_Persona(0) = header_Id_Pers
       Dim header_Patient As New POCD_MT000040Patient
       Dim name As New PN
       Dim nome(0) As String
       Dim nome_p As DataTable = funz.dati_paziente(Id_Paziente, errstr)
       If nome_p.Rows.Count > 0 Then
           nome(0) = nome_p.Rows(0).Item("nome").ToString
       End If
       Dim H_nome As New engiven

       H_nome.Text = nome
       Dim cognome(0) As String
       Dim cognome_p As DataTable = funz.dati_paziente(Id_Paziente, errstr)
       If cognome_p.Rows.Count > 0 Then
           cognome(0) = cognome_p.Rows(0).Item("cognome").ToString
       End If
       Dim H_cognome As New enfamily
       H_cognome.Text = cognome

       Dim elementi(1) As ENXP
       elementi(0) = H_nome
       elementi(1) = H_cognome
       name.Items = elementi


       Dim H_nomi(0) As PN
       H_nomi(0) = name


       Dim gender As New CE
       Dim sesso As DataTable = funz.dati_paziente(Id_Paziente, errstr)
       If sesso.Rows.Count > 0 Then
           If sesso.Rows(0).Item("id_sesso") = 1 Then

               gender.code = "F"
           ElseIf sesso.Rows(0).Item("id_sesso") = 2 Then
               gender.code = "M"
           End If
       End If
       gender.codeSystem = "2.16.840.1.113883.5.1"

       Dim data_nascita As New TS
       Dim data As New Date
       Dim data_n As DataTable = funz.dati_paziente(Id_Paziente, errstr)
       If data_n.Rows.Count > 0 Then
           data = data_n.Rows(0).Item("data_nascita").ToString
```

```
        End If
        Dim data_split(3) As String
        data_split = Split(data, "/")
        Dim gg As String = data_split(0)
        Dim MM As String = data_split(1)
        Dim yyyy As String = data_split(2)

        Dim data_nasc As String = (yyyy & MM & gg)
        data_nascita.value = data_nasc

        header_Patient.classCode = "PSN"
        header_Patient.determinerCode = "INSTANCE"
        header_Patient.name = H_nomi
        header_Patient.administrativeGenderCode = gender
        header_Patient.birthTime = data_nascita
        Dim header_Patient_Role As New POCD_MT000040PatientRole
        header_Patient_Role.classCode = "PAT"
        header_Patient_Role.id = header_Id_Persona
        header_Patient_Role.patient = header_Patient
        Dim record_t As New POCD_MT000040RecordTarget
        record_t.typeCode = "RCT"
        record_t.contextControlCode = "OP"
        record_t.patientRole = header_Patient_Role
        record_t.templateId = header_Id_Persona

        Return record_t
    End Function
```

3.1.2.5.1.12 Author of the letter: <author>

The person who created the document can be identified by one or more <id> elements:

- The fiscal code of the patient (which is mandatory);
- The code assigned by the regional registry (which is optional).

Also in this case only the first will be considered (for the same reasons explained previously), which is defined by the same attributes previously mentioned.

In addition, the element must contain a <time> sub-element, with the indication of the time document production (type TS, consisting of the <value> attribute that we already have view).

Also in this case the implementation above caried out by a function that retrieves the requested data directly from the database:

```
        Dim orario As String = data_split(1)
        Dim offset As String = data_split(2)
        Dim data_giorni_split(3) As String
        data_giorni_split = Split(ggmmaa, "/")
        Dim giorno As String = data_giorni_split(0)
        Dim mese As String = data_giorni_split(1)
        Dim anno As String = data_giorni_split(2)
        Dim ora_split(3) As String
        ora_split = Split(orario, ".")
        Dim ora As String = ora_split(0)
        Dim min As String = ora_split(1)
        Dim sec As String = ora_split(2)
        Dim off_split(2) As String
        off_split = Split(offset, ":")
        Dim off1 As String = off_split(0)
        Dim off2 As String = off_split(1)
    Dim data_compl As String = anno & mese & giorno & ora & min & sec & off1 & off2
        Header_Author_Time.value = data_compl



        Dim Header_Author_AssignedAuthor As New POCD_MT000040AssignedAuthor
        Dim Id_AssigneAuthor As New II
        Dim sessione = funz.dai_id_sessione(Id_Ricovero, errstr)
        Dim id_operatore = funz.dai_id_oper(sessione, errstr)
        Dim tab_char19 As String = funz.dai_CF_operatore(id_operatore, errstr)
        Id_AssigneAuthor.extension = tab_char19.ToString
        Id_AssigneAuthor.root = "2.16.840.1.113883.2.9.4.3.2"

        Dim Header_Id_AssignedAuthor(0) As II
        Header_Id_AssignedAuthor(0) = Id_AssigneAuthor
        Header_Author_AssignedAuthor.id = Header_Id_AssignedAuthor

        Dim Header_Author As New POCD_MT000040Author
        Header_Author.typeCode = "AUT"
        Header_Author.contextControlCode = "OP"
        Header_Author.time = Header_Author_Time
        Header_Author.assignedAuthor = Header_Author_AssignedAuthor

        Return Header_Author
    End Function
```

3.1.2.5.1.13 Preservation of the letter: <custodian>

This element identifies the organization in charge of custody of the original document, corresponding to the registrar of digital assets. This structure is generally the structure to which the creator of the document belongs. This element is represented by a role, <assignedCustodian>, played by an entity represented by the element <representedCustodianOrganization>. This last element must contain an <id> element that reports the identifier of the facility that is responsible for keeping the document. The description of the attributes is shown below:

ATTRIBUTE	TYPE	VALUE	DETAILS
ROOT	OID	[ORGANIZATION IDENTIFICATION DOMAIN OID]	IDENTIFICATION DOMAIN IDENTIFIER OF THE ORGANIZATIONS

EXTENSION	ST	[ORGANIZATION ID]	ORGANIZATION IDENTIFIER (ASL, REGION) BY THE IDENTIFICATION DOMAIN DEFINED IN THE ATTRIBUTE ROOT

Again I created a function to implement this field:

```
Dim Header_Custodian As POCD_MT000040Custodian
Header_Custodian = Crea_Header_Custodian()

 Public Function Crea_Header_Custodian() As POCD_MT000040Custodian


       Dim RCustodianOrganization As New POCD_MT000040CustodianOrganization
       Dim Id_RCustodianOrganization As New II
       Id_RCustodianOrganization.root = "OID VILLA SCASSI"
       Id_RCustodianOrganization.extension = "identificativo dell'organizzazione"

       Dim name As New [ON]
       Dim nome(0) As String
       nome(0) = "ASL 3 Ospedale Villa Scassi"
       name.Text = nome

       Dim Header_Id_RCustodianOrganization(0) As II
       Header_Id_RCustodianOrganization(0) = Id_RCustodianOrganization
       RCustodianOrganization.id = Header_Id_RCustodianOrganization
       RCustodianOrganization.classCode = "ORG"
       RCustodianOrganization.determinerCode = "INSTANCE"
       RCustodianOrganization.name = name


       Dim Header_AssignedCustodian As New POCD_MT000040AssignedCustodian
       Header_AssignedCustodian.classCode = "ASSIGNED"
   Header_AssignedCustodian.representedCustodianOrganization = RCustodianOrganization


       Dim Header_Custodian As New POCD_MT000040Custodian
       Header_Custodian.typeCode = "CST"
       Header_Custodian.assignedCustodian = Header_AssignedCustodian

       Return Header_Custodian
   End Function
```

3.1.2.5.1.14 Signer of the document: <legalAuthenticator>

Element that reports the signer of the document. If the document is generated from a machine, the person responsible for the document is the organization responsible for the document generation. This element must contain a <time> element with the indication of the time when the document was signed, a <signatureCode> element to indicate that the document was signed, and an <assignedEntity> element, intended to accept the <id> element of the responsible physician. The <time> element is composed from the value attribute that we have already described, as well as the id element that it

consists of from the root and extension element which shows the tax code of the signatory of the letter. As for the <signatureCode> element, it consists of the following attribute:

Attribute	Type	Value	Details
Code	ST	“S”	Code indicatig that the documet is signed

The function created for the implementation of this field, which takes the data relating to the doctor who closed the hospitalization and generated the HDLET directly from the database is shown below:

```
Dim Header_LegalAuthenticator As POCD_MT000040LegalAuthenticator
eader_LegalAuthenticator = Crea_Header_legalAuthenticator(Id_Ricovero, errstr)

Public Function Crea_Header_legalAuthenticator(ByVal Id_Ricovero As String, ByRef errstr A
s String)                                                                          As POC
D_MT000040LegalAuthenticator
        Dim LA_Time As New TS
        Dim data_o As DateTimeOffset = Now

        Dim data As String = data_o.ToString
        Dim data_split(3) As String
        data_split = Split(data, " ")
        Dim ggmmaa As String = data_split(0)
        Dim orario As String = data_split(1)
        Dim offset As String = data_split(2)
        Dim data_giorni_split(3) As String
        data_giorni_split = Split(ggmmaa, "/")
        Dim giorno As String = data_giorni_split(0)
        Dim mese As String = data_giorni_split(1)
        Dim anno As String = data_giorni_split(2)
        Dim ora_split(3) As String
        ora_split = Split(orario, ".")
        Dim ora As String = ora_split(0)
        Dim min As String = ora_split(1)
        Dim sec As String = ora_split(2)
        Dim off_split(2) As String
        off_split = Split(offset, ":")
        Dim off1 As String = off_split(0)
        Dim off2 As String = off_split(1)
        Dim data_compl As String = anno & mese & giorno & ora & min & sec & off1 & off2

        LA_Time.value = data_compl

        LA_Time.nullFlavor = "NAV"


        Dim LA_SignatureCode As New CS
        LA_SignatureCode.code = "S"

        Dim LA_AssignedEntity As New POCD_MT000040AssignedEntity
```

```
        LA_AssignedEntity.classCode = "ASSIGNED"
        Dim LA_AE_Id As New II
        LA_AE_Id.root = "2.16.840.1.113883.2.9.4.3.2"
        Dim sessione = funz.dai_id_sessione(Id_Ricovero, errstr)
        Dim id_operatore = funz.dai_id_oper(sessione, errstr)
        Dim tab_char19 As String = funz.dai_CF_operatore(id_operatore, errstr)
        LA_AE_Id.extension = tab_char19.ToString

        Dim LA_AssignedEntity_Id(0) As II
        LA_AssignedEntity_Id(0) = LA_AE_Id
        LA_AssignedEntity.id = LA_AssignedEntity_Id

        Dim Header_LegalAuthenticator As New POCD_MT000040LegalAuthenticator
        Header_LegalAuthenticator.typeCode = "LA"
        Header_LegalAuthenticator.contextControlCode = "OP"
        Header_LegalAuthenticator.time = LA_Time
        Header_LegalAuthenticator.signatureCode = LA_SignatureCode
        Header_LegalAuthenticator.assignedEntity = LA_AssignedEntity

        Return Header_LegalAuthenticator
    End Function
```

3.1.2.5.1.15 Reference hospitalization: <componentOf>

Identifies the hospitalization to which the HDLET refers, is defined by <componentOf> / <encompassingEncounter>. This element contains data such as: identification of the hospitalization, start date and end date of admission, the admission ward and the admission hospital. The hospitalization identifier consists of an <id> element consisting of the attributes:

Attribute	Type	Value	Details
Root	OID	[NOSOLOGICAL COMPANY BRANCH OID]	It represents the OID of the nosological branch of the structure that carries out hospitalization
Extension	ST	[NOSOLOgical number]	Nosological of the recovery
AssigningAuthorityName	ST	[company name]	STRUCTURE NAME THAT DOES THE RECOVERY

The <effectiveTime> element identifies the start and end hospitalization dates, and they must be put in <effectiveTime> / <low> and> effectiveTime> / <high> respectively. Both dates must be encoded within the TS-type value attribute.

Another mandatory element is <healthCareFacility>, which specifies the operating unit that has discharged the patient and has as a path componentof / encompassingEncounter / location / healthCareFacility. The composition of <id> of this element is:

Attribute	Type	Value	Dettails
root	OID	2.16.84.1.13883.2.9.4.1.6	List of Departments (Hospital Structure) to which the operating unit of hospitalization is headed
extension	ST	[OPERATING UNIT CODE]	Structure Code+Sub Internal Structure Code+Discipline Code that represents the operating unit inside that particular domain

The department name is listed in <healthCareFacility> / <location> / <name>. The hospitalization facility, on the other hand, is reported in <healthCareFacility> / <serviceProviderOrganization> / <id>. where the <id> element is characterized by the following attributes:

Attribute	Type	Value	Dettails
root	OID	2.16.84.1.13883.2.9.4.1.2	List of Hospitals to which the operating unit of hospitalization is headed
extension	ST	[PRESIDIO CODE]	Code HSP 11 which represents the hospitalization unit.

Also in this case the element and the sub-elements have been implemented by a function:

```
Dim Header_componentOf As POCD_MT000040Component1
Header_componentOf = Crea_Header_ComponentOf(Id_Ricovero, errstr)

Public Function Crea_Header_ComponentOf(ByVal Id_Ricovero As String, ByRef errstr As Strin
g) As

POCD_MT000040Component1

        Dim data_in As New Date
        Dim inizio As DataTable = funz.dati_ricovero(Id_Ricovero, errstr)
        If inizio.Rows.Count > 0 Then
            data_in = inizio.Rows(0).Item("data_i").ToString
        End If
        Dim data_in_off As DateTimeOffset = data_in
        Dim data1_off As String = data_in_off.ToString
        Dim data_fine As New Date
        Dim fine As DataTable = funz.dati_ricovero(Id_Ricovero, errstr)
        If fine.Rows.Count > 0 Then
            data_fine = fine.Rows(0).Item("data_f").ToString
        End If
        Dim data_fin_off As DateTimeOffset = data_fine
```

```
        Dim data2_off As String = data_in_off.ToString
        Dim data_split(3) As String
        data_split = Split(data1_off, " ")
        Dim ggmmaa As String = data_split(0)
        Dim orario As String = data_split(1)
        Dim offset As String = data_split(2)
        Dim data_giorni_split(3) As String
        data_giorni_split = Split(ggmmaa, "/")
        Dim giorno As String = data_giorni_split(0)
        Dim mese As String = data_giorni_split(1)
        Dim anno As String = data_giorni_split(2)
        Dim ora_split(3) As String
        ora_split = Split(orario, ".")
        Dim ora As String = ora_split(0)
        Dim min As String = ora_split(1)
        Dim sec As String = ora_split(2)
        Dim off_split(2) As String
        off_split = Split(offset, ":")
        Dim off1 As String = off_split(0)
        Dim off2 As String = off_split(1)
        Dim data_compl As String = anno & mese & giorno & ora & min & sec & off1 & off2



        Dim data_split1(3) As String
        data_split1 = Split(data2_off, " ")
        Dim ggmmaa1 As String = data_split1(0)
        Dim orario1 As String = data_split1(1)
        Dim offset1 As String = data_split1(2)
        Dim data_giorni_split1(3) As String
        data_giorni_split1 = Split(ggmmaa1, "/")
        Dim giorno1 As String = data_giorni_split1(0)
        Dim mese1 As String = data_giorni_split1(1)
        Dim anno1 As String = data_giorni_split1(2)
        Dim ora_split1(3) As String
        ora_split1 = Split(orario1, ".")
        Dim ora1 As String = ora_split1(0)
        Dim min1 As String = ora_split1(1)
        Dim sec1 As String = ora_split1(2)
        Dim off_split1(2) As String
        off_split1 = Split(offset1, ":")
        Dim off11 As String = off_split1(0)
        Dim off21 As String = off_split1(1)
    Dim data_compl1 As String = anno1 & mese1 & giorno1 & ora1 & min1 & sec1 & off11 & off21

        Dim ricovero As New IVL_TS

        Dim H_inizio As New IVXB_TS
        H_inizio.value = data_compl

        Dim H_fine As New IVXB_TS
        H_fine.value = data_compl1
```

```
        Dim ricoveri(1) As IVXB_TS
        ricoveri(0) = H_inizio
        ricoveri(1) = H_fine
        ricovero.Items = ricoveri


        Dim ric(1) As ItemsChoiceType2
        ric(0) = ItemsChoiceType2.low
        ric(1) = ItemsChoiceType2.high
        ricovero.ItemsElementName = ric

        Dim id_ric As New II
```

```
        id_ric.root = "2.16.840.1.113883.2.9.2.[RAMO:AZIENDALE.NOSOLOGICI].4.6"
        id_ric.extension = Id_Ricovero
        id_ric.assigningAuthorityName = "ASL 3 Villa Scassi"
        id_ric.displayable = True

        Dim H_C_fac_id As New II
        H_C_fac_id.root = "2.16.840.1.113883.2.9.4.1.6"
        H_C_fac_id.extension = "070301.04.08"
        Dim Header_H_C_id(0) As II
        Header_H_C_id(0) = H_C_fac_id

        Dim name As New EN
        Dim nome(0) As String
        nome(0) = "Reparto di cardiologia"
        name.Text = nome
        Dim location As New POCD_MT000040Place
        location.name = name

        Dim id_org As New II
        id_org.root = "2.16.840.1.113883.2.9.4.1.2"
        id_org.extension = "07030104"
        id_org.assigningAuthorityName = "MINISTERO DELLA SALUTE"
        Dim H_id_org(0) As II
        H_id_org(0) = id_org

        Dim organization As New POCD_MT000040Organization
        organization.id = H_id_org

        Dim H_C_fac As New POCD_MT000040HealthCareFacility
        H_C_fac.id = Header_H_C_id
        H_C_fac.location = location
        H_C_fac.serviceProviderOrganization = organization

        Dim H_id_ric(0) As II
        H_id_ric(0) = id_ric

        Dim H_location As New POCD_MT000040Location
        H_location.healthCareFacility = H_C_fac
        Dim eEncounter As New POCD_MT000040EncompassingEncounter
        eEncounter.classCode = "ENC"
        eEncounter.moodCode = "EVN"
        eEncounter.id = H_id_ric
        eEncounter.location = H_location
        eEncounter.effectiveTime = ricovero

        Dim Header_Component_of As New POCD_MT000040Component1
        Header_Component_of.typeCode = ActRelationshipHasComponent.COMP
        Header_Component_of.encompassingEncounter = eEncounter



        Return Header_Component_of
    End Function
```

3.1.2.5.2 CDA Body of the HDLET document

The CDA standard requires that the body of a document can be formed in a structured or unstructured way. The functions to create the individual sections were first created and subsequently the body was implemented.

The HDLET defined according to the HL7-CDA Rel.2.0 standard requires a body structured in several sections in which it is possible to insert all the information of interest. This kind of document is organized according to a sequence of <section> elements. Right away we can see the sections provided, the relative LOINC coding and the mandatory nature.

Section	LOINC Codes	Description LOINC ShortName	Obligatory
Reason for hospitalization	**46241-6**	**Hospital Admission Dx**	**MANDATORY**
Initial clinical framework. Subsections:	47039-3	Hospital Admission History And PhysicalNote	OPTIONAL
Anamnesis	11329-0	History General	OPTIONAL
Physical Examination	29545-1	Phisical Examination	OPTIONAL
Therapy Drug	42346-7	Medications On Admissin	OPTIONAL
Hospital Course	**8648-8**	**Hospital Course**	**MANDATORY**
Significant findings and investigations, Instrumental investigations Diagnostic	30954-2	Relevant Diagnostic Tests & Or Laboratory Data	OPTIONAL
Procedures performed during hospitalization	29554-3	Procedure	OPTIONAL
Allergies	48765-2	Allergies	OPTIONAL
Drug therapy carried out during the recovery	10160-0	Selected Medicine Administered During Hospitalization	OPTIONAL
Condition of the patient at discharge + diagnosis on discharge	**11535-2**	**Hospital Discharge Dx**	**MANDATORY**
Therapy pharmacological at discharge	10183-2	Discharge Medications	OPTIONAL
Follow-up instructions	18776-5	Treatment Plan	OPTIONAL

The information contained in the letter describes clinical aspects of the hospitalization. Each section must have a <text> element that contains the information human-readable section specifications. Depending of the type <section>, <entry> elements can be provided, partially or totally coded, containing information details such as measurements, interventions, administration of drugs or attachments multimedia. The information content which is present in the coded entries must always be also reported in textual form in the "narrative block" of the section.

Referencing in the narrative part can take place both by the text element and by the value / OriginalText element. Special constraints existing at the entry level can impose the presence of both: the first element (text) describes the information regarding the entry in its entirety (including dates, comments, etc etc); the according to (value / OriginalText) the only concept expressed by the code (e.g. a diagnosis) without the ancillary information such as additional comments, diagnosis status, etc etc.

Example:

```
<component>
   <structuredBody moodCode="EVN" classCode="DOCBODY">
      <component typeCode="COMP">
         <section classCode="DOCSECT" moodCode="EVN">
            <code .../>
            <title>...</title>
            <text>...</text>
            <entry>
               <entryRelationship>...</entryRelationship>
               <entryRelationship>...</entryRelationship>
            </entry>
         </section>
      </component>
      <component typeCode="COMP">
         <section classCode="DOCSECT" moodCode="EVN">
            <code .../>
            <title>...</title>
            <text>...</text>
            <entry>
               <observation>...</observation>
            </entry>
         </section>
      </component>
   </structuredBody>
</component>
```

The translation into VB classes of the sections and entries is shown below.

```
Partial Public Class POCD_MT000040Component2

    Private realmCodeField() As CS

    Private typeIdField As POCD_MT000040InfrastructureRoottypeId

    Private templateIdField() As II

    Private itemField As POCD_MT000040StructuredBody

    Private nullFlavorField As String

    Private typeCodeField As ActRelationshipHasComponent

    Private typeCodeFieldSpecified As Boolean

    Private contextConductionIndField As Boolean

    Private contextConductionIndFieldSpecified As Boolean

    Public Sub New()
        MyBase.New
        Me.typeCodeField = ActRelationshipHasComponent.COMP
        Me.contextConductionIndField = True
```

```
    End Sub
Partial Public Class POCD_MT000040StructuredBody
    Private realmCodeField() As CS
    Private typeIdField As POCD_MT000040InfrastructureRoottypeId
    Private templateIdField() As II
    Private confidentialityCodeField As CE
    Private languageCodeField As CS
    Private componentField() As POCD_MT000040Component3
    Private nullFlavorField As String
    Private classCodeField As String
    Private moodCodeField As String
Partial Public Class POCD_MT000040Component3
    Private realmCodeField() As CS
    Private typeIdField As POCD_MT000040InfrastructureRoottypeId
    Private templateIdField() As II
    Private sectionField As POCD_MT000040Section
    Private nullFlavorField As String
    Private typeCodeField As ActRelationshipHasComponent
    Private typeCodeFieldSpecified As Boolean
    Private contextConductionIndField As Boolean
    Private contextConductionIndFieldSpecified As Boolean
Partial Public Class POCD_MT000040Section
    Private realmCodeField() As CS
    Private typeIdField As POCD_MT000040InfrastructureRoottypeId
    Private templateIdField() As II
    Private idField As II
    Private codeField As CE
    Private titleField As ST
    Private textField As StrucDocText
    Private confidentialityCodeField As CE
    Private languageCodeField As CS
    Private subjectField As POCD_MT000040Subject
    Private authorField() As POCD_MT000040Author
    Private informantField() As POCD_MT000040Informant12
```

```
    Private entryField() As POCD_MT000040Entry

    Private componentField() As POCD_MT000040Component5

    Private idField1 As String

    Private nullFlavorField As String

    Private classCodeField As String

    Private moodCodeField As String

Partial Public Class POCD_MT000040Entry

    Private realmCodeField() As CS

    Private typeIdField As POCD_MT000040InfrastructureRoottypeId

    Private templateIdField() As II

    Private itemField As POCD_MT000040SubstanceAdministration

    Private nullFlavorField As String

    Private typeCodeField As x_ActRelationshipEntry

    Private contextConductionIndField As Boolean

    Private contextConductionIndFieldSpecified As Boolean

Partial Public Class POCD_MT000040EntryRelationship

    Private realmCodeField() As CS

    Private typeIdField As POCD_MT000040InfrastructureRoottypeId

    Private templateIdField() As II

    Private sequenceNumberField As INT

    Private seperatableIndField As BL

    Private itemField As Object

    Private nullFlavorField As String

    Private typeCodeField As x_ActRelationshipEntryRelationship

    Private inversionIndField As Boolean

    Private inversionIndFieldSpecified As Boolean

    Private contextConductionIndField As Boolean

    Private negationIndField As Boolean

    Private negationIndFieldSpecified As Boolean

Partial Public Class POCD_MT000040Observation

    Private realmCodeField() As CS

    Private typeIdField As POCD_MT000040InfrastructureRoottypeId
```

```
    Private templateIdField() As II

    Private idField() As II

    Private codeField As CD

    Private derivationExprField As ST

    Private textField As ED

    Private statusCodeField As CS

    Private effectiveTimeField As IVL_TS

    Private priorityCodeField As CE

    Private repeatNumberField As IVL_INT

    Private languageCodeField As CS

    Private valueField() As ANY

    Private interpretationCodeField() As CE

    Private methodCodeField() As CE

    Private targetSiteCodeField() As CD

    Private subjectField As POCD_MT000040Subject

    Private specimenField() As POCD_MT000040Specimen

    Private performerField() As POCD_MT000040Performer2

    Private authorField() As POCD_MT000040Author

    Private informantField() As POCD_MT000040Informant12

    Private participantField() As POCD_MT000040Participant2

    Private entryRelationshipField() As POCD_MT000040EntryRelationship

    Private referenceField() As POCD_MT000040Reference

    Private preconditionField() As POCD_MT000040Precondition

    Private referenceRangeField() As POCD_MT000040ReferenceRange

    Private nullFlavorField As String

    Private classCodeField As String

    Private moodCodeField As x_ActMoodDocumentObservation

    Private negationIndField As Boolean

    Private negationIndFieldSpecified As Boolean
```

The attestation of conformity can be made not only as one document, but also at the "module" level (section, clinical stetements, entry) within the document itself. Also in this case the certification is made through a reference to an identifier that indicates the adherence of the module to a specific pattern. To certify the adherence of a module of the CDA in the HDLET it is necessary use the templateId element as follows:

```
<section>
  <templateId root="2.16.840.1.113883.2.9.10.2.99.99"/>
   …
  <observation classCode="OBS" moodCode="EVN">
     <templateId root="2.16.840.1.113883.2.9.10.2.99.99.99"/>
     …
  </observation>
</section>
```

3.1.2.5.2.1 Reason for admission

It is a mandatory element that describes the main cause that led to hospitalization of the patient. The section identifier is shown in the qualifying <code> element each section of medical history / physical examination. The encoding that is to be used for specifying the type of section in question is the LOINC code.

Composition of the <code> element:

Attribute	Type	Value	Details
Code	ST	46241-6	Element extracted from the vocabulary used
codeSystem	OID	"2.16.840.1.113883.6.1"	Vocabulary OID used
codeSystemName	ST	"LOINC"	Vocabulary name used
codeSystemVersion	ST	[VERSION]	Vocabulary version used
displayName	ST	Reason for admission	Name of the section or summary description of the information content according to the vocabulary used

The <title> element is mandatory and represents the title of the section. Another element is the narrative block <text>, within which the author of the document must report all "human-readable" information, that is, all information exposed in a manner narrative. This narrative part can also be articulated in order to encode the textual information in section detail, but in my case it was not used because the medical record created includes a free text for this field. So, don't since not even an ICD9-CM encoding is used in the folder for the encoding of this field, not even the entry element was created to describe the diagnosis of admission indicated by an ICD9-CM vocabulary code. In any case, if the aforementioned modification is present, it would be enough to simply implement the attribute <observation> of <entry> as follows:

```
<entry>
   <observation classCode="OBS" moodCode="EVN">
……
    <code code=”8646-2"
        codeSystem="2.16.840.1.113883.6.1" codeSystemName="LOINC"
        displayName=“Diagnosi di Accettazione Ospedaliera” />
…….
    <value xsi:type=”CD” code="[CODICE_ICD9_DIAGNOSI]"
        codeSystem="2.16.840.1.113883.6.103" codeSystemName="ICD9CM"
        displayName="[DESCRIZIONE_DIAGNOSI]">
        <translation code="[CODICE_DIAGNOSI]" codeSystem="2.16.99"
           codeSystemName="Catalogo Ultraspecialisitco Locale"
           displayName="[DESCRIZIONE_DETTAGLIO_DIAGNOSI]"/>
    </code>
  </observation>
</entry>
```

The implementation in this case was:

3.1.2.5.2.2 Initial clinical setting

It is an optional element that allows you to report, in a textual part and in three others structured a series of information relating to the medical history, physical examination and home medical therapy.

The <code> element of this section is composed as follows:

Attribute	Type	Value	Details
Code	ST	47039-3	Element extracted from the vocabulary used
codeSystem	OID	“2.16.840.1.113883.6.1”	Vocabulary OID used
codeSystemName	ST	“LOINC”	Vocabulary name used
codeSystemVersion	ST	[VERSION]	Vocabulary version used
displayName	ST	Initial clinical setting	Name of the section or summary description of the information content according to the vocabulary used

Also in this case the title and the text are present, there are also sub-sections listed below.

3.1.2.5.2.2.1 Medical history

This element groups the information regarding the medical history according to

typology:

- Remote Pathological History
- Next Pathological History

- Physiological history
- Family history

The <code> element is as follows:

Attribute	Type	Value	Details
Code	ST	29545-1	Element extracted from the vocabulary used
codeSystem	OID	“2.16.840.1.113883.6.1”	Vocabulary OID used
codeSystemName	ST	“LOINC”	Vocabulary name used
codeSystemVersion	ST	[VERSION]	Vocabulary version used
displayName	ST	Medical history	Name of the section or summary description of the information content according to the vocabulary used

Also in this case we would have a title and a text field.

3.1.2.5.2.2.2 Physical Exam

It is an optional element that represents the physical examination performed on the patient at the entrance, shown in the narrative block.

The <code> element is as follows:

Attribute	Type	Value	Details
Code	ST	29545-1	Element extracted from the vocabulary used
codeSystem	OID	“2.16.840.1.113883.6.1”	Vocabulary OID used
codeSystemName	ST	“LOINC”	Vocabulary name used
codeSystemVersion	ST	[VERSION]	Vocabulary version used

displayName	ST	Physical Exam	Name of the section or summary description of the information content according to the vocabulary used

3.1.2.5.2.2.3 Pharmacological Therapy at the Entrance

It is an optional element that describes the list of medications the patient was taking access, or medical therapy carried out at home, or medical therapy at the entrance if the patient is not from home.

The <code> element is as follows:

Attribute	Type	Value	Details
Code	ST	423-8	Element extracted from the vocabulary used
codeSystem	OID	"2.16.840.1.113883.6.1"	Vocabulary OID used
codeSystemName	ST	"LOINC"	Vocabulary name used
codeSystemVersion	ST	[VERSION]	Vocabulary version used
displayName	ST	Pharmacological Therapy at the Entrance	Name of the section or summary description of the information content according to the vocabulary used

Below is the function that implements the section and its subsections, the data is retrieved directly from the database:

```
Dim comp3_1 As New POCD_MT000040Component3
     Dim ICI = Crea_Inquadramento_Clinico_Iniziale(Id_Ricovero, errstr)
     comp3_1.section = ICI


Public Function Crea_Inquadramento_Clinico_Iniziale(ByVal Id_Ricovero As String, ByRe
f errstr As String) As POCD_MT000040Section
     Dim Id_Templ_Sezione As New II
     Id_Templ_Sezione.root = "2.16.840.1.113883.2.9.10.2.99.99"
     Dim Im_Sec_Template(0) As II
     Im_Sec_Template(0) = Id_Templ_Sezione

     Dim code_ICI As New CE
     code_ICI.code = "47039-3"
     code_ICI.displayName = "Ricovero Ospedaliero, anamnesi ed esame obiettivo”
     code_ICI.codeSystem = "2.16.840.1.113883.6.1"
     code_ICI.codeSystemName = "LOINC"
     code_ICI.codeSystemVersion = "2.19"


     Dim par_dislip As String = "Dislipidemia"
     Dim id_dislip As Integer = funz.dai_id_par_da_nome(par_dislip)
```

```
    Dim val1 As Integer = funz.dai_valori_elenc_accettazione(Id_Ricovero, id_dislip,
 errstr)
    Dim tab_char1 As DataTable = funz.dai_valori_elenc(val1, errstr)

    Dim par_fam As String = "Familiarità"
    Dim id_fam As Integer = funz.dai_id_par_da_nome(par_fam)
    Dim val2 As Integer = funz.dai_valori_elenc_accettazione(Id_Ricovero, id_fam, er
rstr)
    Dim tab_char2 As DataTable = funz.dai_valori_elenc(val2, errstr)

    Dim par_fumo As String = "Fumo"
    Dim id_fumo As Integer = funz.dai_id_par_da_nome(par_fumo)
    Dim val3 As Integer = funz.dai_valori_elenc_accettazione(Id_Ricovero, id_fumo, e
rrstr)
    Dim tab_char3 As DataTable = funz.dai_valori_elenc(val3, errstr)

    Dim par_ipert As String = "Ipertensione"
    Dim id_ipert As Integer = funz.dai_id_par_da_nome(par_ipert)
    Dim val4 As Integer = funz.dai_valori_elenc_accettazione(Id_Ricovero, id_ipert,
errstr)
    Dim tab_char4 As DataTable = funz.dai_valori_elenc(val4, errstr)

    Dim par_diab As String = "Diabete"
    Dim id_diab As Integer = funz.dai_id_par_da_nome(par_diab)
    Dim val5 As Integer = funz.dai_valori_elenc_accettazione(Id_Ricovero, id_diab, e
rrstr)
    Dim tab_char5 As DataTable = funz.dai_valori_elenc(val5, errstr)
    Dim par_ie As String = "Insufficienza Epatica"
    Dim id_ie As Integer = funz.dai_id_par_da_nome(par_ie)
    Dim val02 As Integer = funz.dai_valori_elenc_accettazione(Id_Ricovero, id_ie, er
rstr)
    Dim tab_char02 As DataTable = funz.dai_valori_elenc(val02, errstr)
    Dim par_ir As String = "Insufficienza Renale"
    Dim id_ir As Integer = funz.dai_id_par_da_nome(par_ir)
    Dim val01 As Integer = funz.dai_valori_elenc_accettazione(Id_Ricovero, id_ir, er
rstr)
    Dim tab_char01 As DataTable = funz.dai_valori_elenc(val01, errstr)
    Dim disp1 As String = ""

    Dim fam As String = ""
    Dim fum As String = ""
    Dim ipe As String = ""
    Dim dia As String = ""
    Dim ie As String = ""
    Dim ir As String = ""

    If tab_char1.Rows.Count > 0 Then
        disp1 = tab_char1.Rows(0).Item("NOME_VALORE").ToString

    End If
    If tab_char2.Rows.Count > 0 Then
        fam = tab_char2.Rows(0).Item("NOME_VALORE").ToString
    End If
    If tab_char3.Rows.Count > 0 Then
        fum = tab_char3.Rows(0).Item("NOME_VALORE").ToString
    End If
    If tab_char4.Rows.Count > 0 Then
        ipe = tab_char4.Rows(0).Item("NOME_VALORE").ToString
    End If
    If tab_char5.Rows.Count > 0 Then
        dia = tab_char5.Rows(0).Item("NOME_VALORE").ToString
    End If
    If tab_char01.Rows.Count > 0 Then
        ir = tab_char01.Rows(0).Item("NOME_VALORE").ToString
    End If
    If tab_char02.Rows.Count > 0 Then
        ie = tab_char02.Rows(0).Item("NOME_VALORE").ToString
```

```
    End If
    Dim titolo(0) As String
    titolo(0) = "Inquadramento Clinico Iniziale"

    Dim titolo_ICI As New ST
    titolo_ICI.Text = titolo

    Dim testo(7) As String
    If tab_char1.Rows.Count > 0 Then
        testo(0) = vbCrLf & par_dislip & ":" & disp1 & "." & vbCrLf
    End If
    If tab_char2.Rows.Count > 0 Then
        testo(1) = par_fam & ":" & fam & "." & vbCrLf
    End If
    If tab_char3.Rows.Count > 0 Then
        testo(2) = par_fumo & ":" & fum & "." & vbCrLf
    End If
    If tab_char4.Rows.Count > 0 Then
        testo(3) = par_ipert & ":" & ipe & "." & vbCrLf
    End If
    If tab_char5.Rows.Count > 0 Then
        testo(4) = par_diab & ":" & dia & "." & vbCrLf
    End If
    If tab_char02.Rows.Count > 0 Then
        testo(5) = par_ie & ":" & ie & "." & vbCrLf
    End If
    If tab_char01.Rows.Count > 0 Then
        testo(6) = par_ir & ":" & ir & "." & vbCrLf
    End If
    Dim testo_ICI As New StrucDocText
    testo_ICI.Text = testo



    Dim code_AG As New CE
    code_AG.code = "11329-0"
    code_AG.displayName = "Anamnesi Generale”
    code_AG.codeSystem = "2.16.840.1.113883.6.1"
    code_AG.codeSystemName = "LOINC"
    code_AG.codeSystemVersion = "2.19"


    Dim titolo1(0) As String
    titolo1(0) = "Anamnesi Generale"

    Dim titolo_AG As New ST
    titolo_AG.Text = titolo1
    Dim AR As String = ""
    Dim AREM As String = ""
    Dim par_anamnesi_rec As String = "Anamnesi Recente"
    Dim id_anam_rec As Integer = funz.dai_id_par_da_nome(par_anamnesi_rec)
    Dim tab_char6 As DataTable = funz.dai_valori_CHAR_per_modifica_accettazione(Id_R
icovero,
id_anam_rec, errstr)
    If tab_char6.Rows.Count > 0 Then
        AR = tab_char6.Rows(0).Item("valore").ToString
    End If
    Dim par_anamnesi_rem As String = "Anamnesi Remota"
    Dim id_anam_rem As Integer = funz.dai_id_par_da_nome(par_anamnesi_rem)
    Dim tab_char7 As DataTable = funz.dai_valori_CHAR_per_modifica_accettazione(Id_R
icovero,
id_anam_rem, errstr)
    If tab_char7.Rows.Count > 0 Then
        AREM = tab_char7.Rows(0).Item("valore").ToString
    End If
    Dim testo1(2) As String
```

```
    If tab_char6.Rows.Count > 0 Then
        testo1(0) = vbCrLf & par_anamnesi_rec & ":" & AR & vbCrLf
    End If
    If tab_char7.Rows.Count > 0 Then
        testo1(1) = par_anamnesi_rem & ":" & AREM & vbCrLf
    End If
    Dim testo_AG As New StrucDocText
    testo_AG.Text = testo1
    Dim Id_Templ_Sezione_AG As New II
    Id_Templ_Sezione_AG.root = "2.16.840.1.113883.2.9.10.2.99.99"
    Dim Im_Sec_Template_AG(0) As II
    Im_Sec_Template_AG(0) = Id_Templ_Sezione_AG

    Dim sezione_AG As New POCD_MT000040Section
    sezione_AG.classCode = "DOCSECT"
    sezione_AG.moodCode = "EVN"
    sezione_AG.templateId = Im_Sec_Template_AG
    sezione_AG.code = code_AG
    sezione_AG.title = titolo_AG
    sezione_AG.text = testo_AG

    Dim code_EO As New CE
    code_EO.code = "29545-1"
    code_EO.displayName = "Esame Obiettivo”
    code_EO.codeSystem = "2.16.840.1.113883.6.1"
    code_EO.codeSystemName = "LOINC"
    code_EO.codeSystemVersion = "2.19"


    Dim titolo2(0) As String
    titolo2(0) = "Esame Obiettivo"

    Dim titolo_EO As New ST
    titolo_EO.Text = titolo2

    Dim par_edemi As String = "Edemi"
    Dim id_edemi As Integer = funz.dai_id_par_da_nome(par_edemi)
Dim val_edemi As Integer = funz.dai_valori_elenc_accettazione(Id_Ricovero, id_edemi,
errstr)
    Dim tab_char9 As DataTable = funz.dai_valori_elenc(val_edemi, errstr)
    Dim edem As String = ""
    If tab_char9.Rows.Count > 0 Then
        edem = tab_char9.Rows(0).Item("NOME_VALORE").ToString
    End If
    Dim edem_altro As String = "Edemi altro"
    Dim id_edem_altro As Integer = funz.dai_id_par_da_nome(edem_altro)
    Dim tab_val_21 As DataTable = funz.dai_valori_CHAR_per_modifica_accettazione(Id_
Ricovero,                                                                    id_ed
em_altro, errstr)
    Dim ede_altro As String = ""
    If tab_val_21.Rows.Count > 0 Then
        ede_altro = tab_val_21.Rows(0).Item("valore").ToString
    End If
    Dim edemi As String
    If (ede_altro IsNot "" And edem = "Altro") Then
        edemi = ede_altro

    ElseIf ede_altro IsNot "" Then
        edemi = edem & ":" & ede_altro
    Else
        edemi = edem
    End If
    Dim par_dec As String = "Decubito"
    Dim id_dec As Integer = funz.dai_id_par_da_nome(par_dec)
    Dim val_dec As Integer = funz.dai_valori_elenc_accettazione(Id_Ricovero, id_dec,
errstr)
    Dim tab_char19 As DataTable = funz.dai_valori_elenc(val_dec, errstr)
```

```
    Dim decu As String = ""
    If tab_char19.Rows.Count > 0 Then
        decu = tab_char19.Rows(0).Item("NOME_VALORE").ToString
    End If
    Dim decub_altro As String = "Decubito altro"
    Dim id_decu_altro As Integer = funz.dai_id_par_da_nome(decub_altro)
   Dim tab_val_ch1 As DataTable = funz.dai_valori_CHAR_per_modifica_accettazione(Id_
Ricovero,                                                                    id_d
ecu_altro, errstr)
    Dim dec_altro As String = ""
    If tab_val_ch1.Rows.Count > 0 Then
        dec_altro = tab_val_ch1.Rows(0).Item("valore").ToString
    End If

    Dim decubito As String
    If (dec_altro IsNot "" And decu = "Altro") Then
        decubito = dec_altro

    ElseIf dec_altro IsNot "" Then
        decubito = decu & ":" & dec_altro
    Else
        decubito = decu
    End If
    Dim par_cute As String = "Cute"
    Dim id_cute As Integer = funz.dai_id_par_da_nome(par_cute)
   Dim val_cute As Integer = funz.dai_valori_elenc_accettazione(Id_Ricovero, id_cute
, errstr)
    Dim tab_char10 As DataTable = funz.dai_valori_elenc(val_cute, errstr)
    Dim cute As String = ""
    If tab_char10.Rows.Count > 0 Then
        cute = tab_char10.Rows(0).Item("NOME_VALORE").ToString
    End If
    Dim cute_altro As String = "Cute altro"
    Dim id_cute_altro As Integer = funz.dai_id_par_da_nome(cute_altro)
    Dim tab_val_22 As DataTable = funz.dai_valori_CHAR_per_modifica_accettazione(Id_
Ricovero,                                                                    id_cu
te_altro, errstr)
    Dim cut_altro As String = ""
    If tab_val_22.Rows.Count > 0 Then
        cut_altro = tab_val_22.Rows(0).Item("valore").ToString
    End If
    Dim cute1 As String
    If (cut_altro IsNot "" And cute = "Altro") Then
        cute1 = cut_altro
    ElseIf cut_altro IsNot "" Then
        cute1 = cute & ":" & cut_altro
    Else cute1 = cute
    End If

    Dim par_sensorio As String = "Sensorio"
    Dim id_sensorio As Integer = funz.dai_id_par_da_nome(par_sensorio)
   Dim val_sensorio As Integer = funz.dai_valori_elenc_accettazione(Id_Ricovero, id_
sensorio, errstr)

    Dim tab_char11 As DataTable = funz.dai_valori_elenc(val_sensorio, errstr)
    Dim sens As String = ""
    If tab_char11.Rows.Count > 0 Then
        sens = tab_char11.Rows(0).Item("NOME_VALORE").ToString
    End If
    Dim sens_altro As String = "Sensorio altro"
    Dim id_sens_altro As Integer = funz.dai_id_par_da_nome(sens_altro)
    Dim tab_val_23 As DataTable = funz.dai_valori_CHAR_per_modifica_accettazione(Id_
Ricovero,id_sens_altro, errstr)
    Dim sensor_altro As String = ""
    If tab_val_23.Rows.Count > 0 Then
        sensor_altro = tab_val_23.Rows(0).Item("valore").ToString
    End If
```

```
    Dim sensorio As String
    If (sensor_altro IsNot "" And sens = "Altro") Then
        sensorio = sensor_altro
    ElseIf sensor_altro IsNot "" Then
        sensorio = sens & ":" & sensor_altro
    Else
        sensorio = sens
    End If
    Dim par_palpazione As String = "Palpazione"
    Dim id_palp As Integer = funz.dai_id_par_da_nome(par_palpazione)
  Dim val_palp As Integer = funz.dai_valori_elenc_accettazione(Id_Ricovero, id_palp,
errstr)
    Dim tab_char30 As DataTable = funz.dai_valori_elenc(val_palp, errstr)
    Dim palp As String = ""
    If tab_char30.Rows.Count > 0 Then
        palp = tab_char30.Rows(0).Item("NOME_VALORE").ToString
    End If
    Dim palp_altro As String = "Palpazione altro"
    Dim id_palp_altro As Integer = funz.dai_id_par_da_nome(palp_altro)
   Dim tab_val_ch5 As DataTable = funz.dai_valori_CHAR_per_modifica_accettazione(Id_
Ricovero,
id_palp_altro, errstr)

    Dim altro_palp As String = ""
    If tab_val_ch5.Rows.Count > 0 Then
        altro_palp = tab_val_ch5.Rows(0).Item("valore").ToString
    End If


    Dim palp1 As String
    If (altro_palp IsNot "" And palp = "Altro") Then
        palp1 = altro_palp
    ElseIf altro_palp IsNot "" Then
        palp1 = palp & ":" & altro_palp
    Else
        palp1 = palp
    End If

    Dim par_fegato As String = "Fegato"
    Dim id_fegato As Integer = funz.dai_id_par_da_nome(par_fegato)
      Dim val_fegato As Integer = funz.dai_valori_elenc_accettazione(Id_Ricovero, id
_fegato,
         errstr)
    Dim tab_char13 As DataTable = funz.dai_valori_elenc(val_fegato, errstr)
    Dim feg As String = ""
    If tab_char13.Rows.Count > 0 Then
        feg = tab_char13.Rows(0).Item("NOME_VALORE").ToString
    End If

    Dim feg_altro As String = "Fegato altro"
    Dim id_feg_altro As Integer = funz.dai_id_par_da_nome(feg_altro)
   Dim tab_val_ch6 As DataTable = funz.dai_valori_CHAR_per_modifica_accettazione(Id_
Ricovero,                                                                    id_f
eg_altro, errstr)
    Dim altro_fegato As String = ""
    If tab_val_ch6.Rows.Count > 0 Then
        altro_fegato = tab_val_ch6.Rows(0).Item("valore").ToString
    End If

    Dim fegato As String
    If (altro_fegato IsNot "" And feg = "Altro") Then
        fegato = altro_fegato
    ElseIf altro_fegato IsNot "" Then
        fegato = feg & ":" & altro_fegato
    Else
        fegato = feg
    End If
```

```
    Dim par_isp As String = "Ispezione e palpazione"
    Dim id_isp As Integer = funz.dai_id_par_da_nome(par_isp)
    Dim val_isp As Integer = funz.dai_valori_elenc_accettazione(Id_Ricovero, id_isp,
 errstr)
    Dim tab_char14 As DataTable = funz.dai_valori_elenc(val_isp, errstr)
    Dim ispez As String = ""
    If tab_char14.Rows.Count > 0 Then
        ispez = tab_char14.Rows(0).Item("NOME_VALORE").ToString
    End If
    Dim ispe_altro As String = "Ispezione e palpazione altro"
    Dim id_ispe_altro As Integer = funz.dai_id_par_da_nome(ispe_altro)
   Dim tab_val_ch7 As DataTable = funz.dai_valori_CHAR_per_modifica_accettazione(Id_
Ricovero,                                                                    id_i
spe_altro, errstr)
    Dim isp_altro As String = ""
    If tab_val_ch7.Rows.Count > 0 Then

        isp_altro = tab_val_ch7.Rows(0).Item("valore").ToString
    End If

    Dim ispezione As String
    If (isp_altro IsNot "" And ispez = "Altro") Then
        ispezione = altro_fegato
    ElseIf isp_altro IsNot "" Then
        ispezione = ispez & ":" & isp_altro
    Else
        ispezione = ispez
    End If

    Dim par_perc As String = "Percussione"
    Dim id_perc As Integer = funz.dai_id_par_da_nome(par_perc)
   Dim val_perc As Integer = funz.dai_valori_elenc_accettazione(Id_Ricovero, id_perc
, errstr)
    Dim tab_char15 As DataTable = funz.dai_valori_elenc(val_perc, errstr)
    Dim perc As String = ""
    If tab_char15.Rows.Count > 0 Then
        perc = tab_char15.Rows(0).Item("NOME_VALORE").ToString
    End If



    Dim percus_altro As String = "Percussione altro"
    Dim id_percus_altro As Integer = funz.dai_id_par_da_nome(percus_altro)
   Dim tab_val_ch8 As DataTable = funz.dai_valori_CHAR_per_modifica_accettazione(Id_
Ricovero,                                                                    id_perc
us_altro, errstr)
    Dim altro_percus As String = ""
    If tab_val_ch8.Rows.Count > 0 Then
        altro_percus = tab_val_ch8.Rows(0).Item("valore").ToString
    End If

    Dim percussione As String
    If (altro_percus IsNot "" And perc = "Altro") Then
        percussione = altro_percus
    ElseIf altro_percus IsNot "" Then
        percussione = perc & ":" & altro_percus
    Else
        percussione = perc
    End If

    Dim par_ascoltazione As String = "Ascoltazione torace"
    Dim id_ascoltazione As Integer = funz.dai_id_par_da_nome(par_ascoltazione)
    Dim val_ascoltazione As Integer = funz.dai_valori_elenc_accettazione(Id_Ricovero
,

id_ascoltazione, errstr)
```

```
    Dim tab_char16 As DataTable = funz.dai_valori_elenc(val_ascoltazione, errstr)
    Dim asc As String = ""
    If tab_char16.Rows.Count > 0 Then
        asc = tab_char16.Rows(0).Item("NOME_VALORE").ToString
    End If

    Dim ascolt_altro As String = "Ascoltazione torace altro"
    Dim id_ascol_altro As Integer = funz.dai_id_par_da_nome(ascolt_altro)
   Dim tab_val_ch9 As DataTable = funz.dai_valori_CHAR_per_modifica_accettazione(Id_
Ricovero,                                                                    id_as
col_altro, errstr)
    Dim ascol_altro As String = ""
    If tab_val_ch9.Rows.Count > 0 Then

        ascol_altro = tab_val_ch9.Rows(0).Item("valore").ToString
    End If

    Dim ascoltazione As String
    If (ascol_altro IsNot "" And asc = "Altro") Then
        ascoltazione = ascol_altro
    ElseIf ascol_altro IsNot "" Then
        ascoltazione = asc & ":" & ascol_altro
    Else
        ascoltazione = asc
    End If

    Dim par_asc As String = "Ascoltazione app cardio toni"
    Dim id_asc As Integer = funz.dai_id_par_da_nome(par_asc)
    Dim val_asc As Integer = funz.dai_valori_elenc_accettazione(Id_Ricovero, id_asc,
 errstr)
    Dim tab_char17 As DataTable = funz.dai_valori_elenc(val_asc, errstr)
    Dim ascolta As String = ""
    If tab_char17.Rows.Count > 0 Then
        ascolta = tab_char17.Rows(0).Item("NOME_VALORE").ToString
    End If

    Dim ascolt_cardio_altro As String = "Ascoltazione app cardio toni altro"
    Dim id_ascol_cardio_altro As Integer = funz.dai_id_par_da_nome(ascolt_cardio_alt
ro)
  Dim tab_val_chasc As DataTable = funz.dai_valori_CHAR_per_modifica_accettazione(Id_
Ricovero,                                                          id_ascol_cardio
_altro, errstr)
    Dim asc_card1 As String = ""
    If tab_val_chasc.Rows.Count > 0 Then
        asc_card1 = tab_val_chasc.Rows(0).Item("valore").ToString
    End If

    Dim asco_toni As String
    If (asc_card1 IsNot "" And ascolta = "Altro") Then
        asco_toni = asc_card1
    ElseIf asc_card1 IsNot "" Then
        asco_toni = ascolta & ":" & asc_card1
    Else
        asco_toni = ascolta
    End If


    Dim par_asc2 As String = "Ascoltazione app cardio soffi"
    Dim id_asc2 As Integer = funz.dai_id_par_da_nome(par_asc2)
   Dim val_asc2 As Integer = funz.dai_valori_elenc_accettazione(Id_Ricovero, id_asc2
, errstr)
    Dim tab_char40 As DataTable = funz.dai_valori_elenc(val_asc2, errstr)
    Dim ascolta2 As String = ""
    If tab_char40.Rows.Count > 0 Then
        ascolta2 = tab_char40.Rows(0).Item("NOME_VALORE").ToString
    End If
```

```
    Dim ascolt_cardio_altro2 As String = "Ascoltazione app cardio soffi altro"
    Dim id_ascol_cardio_altro2 As Integer = funz.dai_id_par_da_nome(ascolt_cardio_al
tro2)
 Dim tab_val_chasc2 As DataTable = funz.dai_valori_CHAR_per_modifica_accettazione(Id_
Ricovero,                                                                id_ascol_cardi
o_altro2, errstr)
    Dim asc_card2 As String = ""
    If tab_val_chasc2.Rows.Count > 0 Then
        asc_card2 = tab_val_chasc2.Rows(0).Item("valore").ToString
    End If

    Dim asco_toni2 As String
    If (asc_card2 IsNot "" And ascolta2 = "Altro") Then
        asco_toni2 = asc_card2
    ElseIf asc_card2 IsNot "" Then
        asco_toni2 = ascolta2 & ":" & asc_card2
    Else
        asco_toni2 = ascolta2
    End If

    Dim par_polsi As String = "Polsi periferici"
    Dim id_polsi As Integer = funz.dai_id_par_da_nome(par_polsi)
  Dim val_polsi As Integer = funz.dai_valori_elenc_accettazione(Id_Ricovero, id_polsi
, errstr)
    Dim tab_char18 As DataTable = funz.dai_valori_elenc(val_polsi, errstr)
    Dim pol_per As String = ""
    If tab_char18.Rows.Count > 0 Then
        pol_per = tab_char18.Rows(0).Item("NOME_VALORE").ToString
    End If

    Dim polsi_altro As String = "Polsi periferici altro"
    Dim id_polsi_altro As Integer = funz.dai_id_par_da_nome(polsi_altro)
   Dim tab_val_ch10 As DataTable = funz.dai_valori_CHAR_per_modifica_accettazione(Id_
Ricovero,
 id_polsi_altro, errstr)
    Dim pols As String = ""
    If tab_val_ch10.Rows.Count > 0 Then
        pols = tab_val_ch10.Rows(0).Item("valore").ToString
    End If

    Dim polsi As String
    If (pols IsNot "" And pol_per = "Altro") Then
        polsi = pols
    ElseIf pols IsNot "" Then
        polsi = pol_per & ":" & pols
    Else
        polsi = pol_per
    End If

    Dim par_Pressione As String = "Pressione Massima"
    Dim id_pressione As Integer = funz.dai_id_par_da_nome(par_Pressione)
  Dim tab_val_ch11 As DataTable = funz.dai_valori_FLOAT_per_modifica_accettazione(Id_
Ricovero,                                                                  id_p
ressione, errstr)
    Dim min As String = ""
    If tab_val_ch11.Rows.Count > 0 Then
        min = tab_val_ch11.Rows(0).Item("valore").ToString
    End If
    Dim par_Press As String = "Pressione Minima"
    Dim id_press As Integer = funz.dai_id_par_da_nome(par_Press)
  Dim tab_val_ch12 As DataTable = funz.dai_valori_FLOAT_per_modifica_accettazione(Id_
Ricovero,                                                                  i
d_press, errstr)
    Dim max As String = ""
    If tab_val_ch12.Rows.Count > 0 Then
        max = tab_val_ch12.Rows(0).Item("valore").ToString
    End If
```

```
    Dim pressione As String = ""
    pressione = min & "/" & max

    Dim par_freq As String = "Frequenza cardiaca"
    Dim id_freq As Integer = funz.dai_id_par_da_nome(par_freq)
  Dim tab_val_ch13 As DataTable = funz.dai_valori_FLOAT_per_modifica_accettazione(Id_
Ricovero,
id_freq, errstr)
    Dim fre As String = ""
    If tab_val_ch13.Rows.Count > 0 Then
        fre = tab_val_ch13.Rows(0).Item("valore").ToString
    End If

    Dim Id_Templ_Sezione_EO As New II
    Id_Templ_Sezione_EO.root = "2.16.840.1.113883.2.9.10.2.99.99"
    Dim Im_Sec_Template_EO(0) As II
    Im_Sec_Template_EO(0) = Id_Templ_Sezione_EO

    Dim testo2(3) As String
    testo2(0) = "Generale" & ": " & par_edemi & " " & edemi & "; " & par_dec & " " &
 decubito & "; " & par_cute & " " & cute1 & "; " & par_sensorio & " " & sensorio & vb
CrLf
    testo2(1) = "Addome" & ": " & par_palpazione & " " & palp1 & "; " & par_fegato &
 " " & fegato & vbCrLf
    testo2(2) = "Torace" & ": " & par_isp & " " & ispezione & "; " & par_perc & " "
& percussione & "; " & par_ascoltazione & " " & ascoltazione & vbCrLf
    testo2(3) = "Apparato Cardiovascolare" & ": " & "Pressione" & " " & pressione &
" mmHg" & "; " & par_freq & " " & fre & " bpm" & "; " & "Ascoltazione Toni" & " " & a
sco_toni & "; " & "Ascoltazione Soffi" & " " & asco_toni2 & "; " & "Polsi Periferici"
 & " " & polsi & vbCrLf
    Dim testo_EO As New StrucDocText
    testo_EO.Text = testo2
    Dim sezione_EO As New POCD_MT000040Section
    sezione_EO.classCode = "DOCSECT"
    sezione_EO.moodCode = "EVN"
    sezione_EO.templateId = Im_Sec_Template_EO
    sezione_EO.code = code_EO
    sezione_EO.title = titolo_EO
    sezione_EO.text = testo_EO

    Dim code_TP As New CE
    code_TP.code = "42346-7"
    code_TP.displayName = "Terapia Farmacologica all'ingresso"
    code_TP.codeSystem = "2.16.840.1.113883.6.1"
    code_TP.codeSystemName = "LOINC"
    code_TP.codeSystemVersion = "2.19"
    Dim titolo3(0) As String
    titolo3(0) = "Terapia Farmacologica all'Ingresso"
    Dim titolo_TP As New ST
    titolo_TP.Text = titolo3
    Dim par_terap As String = "Terapia Pregressa"
    Dim id_terap As Integer = funz.dai_id_par_da_nome(par_terap)
  Dim tab_char2bis As DataTable = funz.dai_valori_CHAR_per_modifica_accettazione
  (Id_Ricovero, id_terap, errstr)
    Dim terapia_p As String = ""
    If tab_char2bis.Rows.Count > 0 Then
        terapia_p = tab_char2bis.Rows(0).Item("valore").ToString
    End If
    Dim testo3(0) As String
    testo3(0) = terapia_p
    Dim Id_Templ_Sezione_TP As New II
    Id_Templ_Sezione_TP.root = "2.16.840.1.113883.2.9.10.2.99.99"
    Dim Im_Sec_Template_TP(0) As II
    Im_Sec_Template_TP(0) = Id_Templ_Sezione_TP
    Dim testo_TP As New StrucDocText
    testo_TP.Text = testo3
    Dim sezione_TP As New POCD_MT000040Section
```

```
    sezione_TP.classCode = "DOCSECT"
    sezione_TP.moodCode = "EVN"
    sezione_TP.templateId = Im_Sec_Template_TP
    sezione_TP.code = code_TP
    sezione_TP.title = titolo_TP
    sezione_TP.text = testo_TP

    Dim component_ICI2 As New POCD_MT000040Component5
    component_ICI2.typeCodeSpecified = ActRelationshipHasComponent.COMP
    component_ICI2.contextConductionInd = True
    component_ICI2.section = sezione_EO
    Dim component_ICI As New POCD_MT000040Component5
    component_ICI.typeCodeSpecified = ActRelationshipHasComponent.COMP
    component_ICI.contextConductionInd = True
    component_ICI.section = sezione_AG
    Dim component_ICI3 As New POCD_MT000040Component5
    component_ICI3.typeCodeSpecified = ActRelationshipHasComponent.COMP
    component_ICI3.contextConductionInd = True
    component_ICI3.section = sezione_TP

    Dim com_ICI(2) As POCD_MT000040Component5
    com_ICI(0) = component_ICI
    com_ICI(1) = component_ICI2
    com_ICI(2) = component_ICI3


    Dim sezione_ICI As New POCD_MT000040Section
    sezione_ICI.classCode = "DOCSECT"
    sezione_ICI.moodCode = "EVN"
    sezione_ICI.templateId = Im_Sec_Template
    sezione_ICI.code = code_ICI
    sezione_ICI.title = titolo_ICI
    sezione_ICI.text = testo_ICI
    sezione_ICI.component = com_ICI

    Return sezione_ICI
End Function
```

3.1.2.5.3 Hospital Course

It is a mandatory element which is designed to describe the progress of the hospitalization, the therapeutic path, and the rehabilitative or assistance diagnostics. The <code> element in this case is composed as follows:

Attribute	Type	Value	Details
Code	ST	8648-8	Element extracted from the vocabulary used
codeSystem	OID	“2.16.840.1.113883.6.1”	Vocabulary OID used
codeSystemName	ST	“LOINC”	Vocabulary name used
codeSystemVersion	ST	[VERSION]	Vocabulary version used
displayName	ST	Hospital Course	Name of the section or summary description of the information content according to the vocabulary used

Also in this case a title and a text field have to be entered. This is done by a function that loads all the admission notes that are present in the database:

```
Dim comp3_2 As New POCD_MT000040Component3
       Dim Decorso_Ospedaliero As New POCD_MT000040Section
       comp3_2.section = Crea_Decorso_Ospedaliero(Id_Ricovero, errstr)

Public Function Crea_Decorso_Ospedaliero(ByVal Id_Ricovero As String, ByRef errstr As
 String) As POCD_MT000040Section
        Dim Id_Templ_Sezione_DO As New II
        Id_Templ_Sezione_DO.root = "2.16.840.1.113883.2.9.10.2.99.99"
        Dim Im_Sec_Template(0) As II
        Im_Sec_Template(0) = Id_Templ_Sezione_DO

       Dim code_DO As New CE
       code_DO.code = "8648-8"
       code_DO.displayName = "Decorso ospedaliero"
       code_DO.codeSystem = "2.16.840.1.113883.6.1"
       code_DO.codeSystemName = "LOINC"
       code_DO.codeSystemVersion = "2.19"


       Dim titolo(0) As String
       titolo(0) = "Decorso Ospedaliero"

       Dim titolo_DO As New ST
       titolo_DO.Text = titolo

       Dim annotazioni As DataTable = funz.Carica_annotazioni(Id_Ricovero)
       Dim test(annotazioni.Rows.Count) As String

       For i = 0 To annotazioni.Rows.Count - 1
           Dim data_ann As Date = annotazioni.Rows(i).Item("data_annotazione")
           Dim datas4 As String
           Dim data_split4(3) As String
           data_split4 = Split(data_ann, "/")
           Dim gg As String = data_split4(0)
           Dim MM As String = data_split4(1)
           Dim anno_ora As String = data_split4(2)
           Dim anno_ora_split2(2) As String
           anno_ora_split2 = Split(anno_ora, " ")
           Dim yyyy As String = anno_ora_split2(0)
           datas4 = CDate(gg & "/" & MM & "/" & yyyy)
           Dim ann As String
           ann = datas4 & "  " & annotazioni.Rows(i).Item("ora_annotaz").ToString &
           "  " & annotazioni.Rows(i).Item("annotazione").ToString

           test(i) = vbCrLf & ann & vbCrLf
       Next

       Dim testo_DO As New StrucDocText
       testo_DO.Text = test




       Dim sezione_DO As New POCD_MT000040Section
```

```
         sezione_DO.classCode = "DOCSECT"
         sezione_DO.moodCode = "EVN"
         sezione_DO.templateId = Im_Sec_Template
         sezione_DO.code = code_DO
         sezione_DO.title = titolo_DO
         sezione_DO.text = testo_DO

         Return sezione_DO
     End Function
```

3.1.2.5.4 Allergy

It is an optional element describing allergies or adverse reactions to active ingredients pharmaceuticals, food or allergens in general.

The <code> element is as follows:

Attribute	Type	Value	Details
Code	ST	48765-2	Element extracted from the vocabulary used
codeSystem	OID	“2.16.840.1.113883.6.1”	Vocabulary OID used
codeSystemName	ST	“LOINC”	Vocabulary name used
codeSystemVersion	ST	[VERSION]	Vocabulary version used
displayName	ST	Allergy section	Name of the section or summary description of the information content according to the vocabulary used

The implementation function is shown below:

```
Dim comp3_3 As New POCD_MT000040Component3
        Dim Allergie As New POCD_MT000040Section
        Allergie = Crea_Sezione_Allergie(Id_Ricovero, errstr)
        comp3_3.section = Allergie

Public Function Crea_Sezione_Allergie(ByVal Id_Ricovero As String, ByRef
errstr As String) As POCD_MT000040Section
        Dim Id_Templ_Sezione_SE As New II
        Id_Templ_Sezione_SE.root = "2.16.840.1.113883.2.9.10.2.99.99"
        Dim Im_Sec_Template(0) As II
        Im_Sec_Template(0) = Id_Templ_Sezione_SE

        Dim code_SE As New CE
        code_SE.code = "48765-2"
        code_SE.displayName = "ALLERGIE E/O REAZIONI AVVERSE"
        code_SE.codeSystem = "2.16.840.1.113883.6.1"
        code_SE.codeSystemName = "LOINC"
        code_SE.codeSystemVersion = "2.19"
```

```
        Dim titolo(0) As String
        titolo(0) = "Allergie e/o Reazioni Avverse"

        Dim titolo_SE As New ST
        titolo_SE.Text = titolo
        Dim par_allergie_altro As String = "Allergie a farmaci altro"
        Dim id_all_altro As Integer = funz.dai_id_par_da_nome(par_allergie_altro)
        Dim tab_val_ch As DataTable = funz.dai_valori_CHAR_per_modifica_accettazione
        (Id_Ricovero, id_all_altro, errstr)
        Dim allergie As String = ""
        If CInt(tab_val_ch.Rows.Count) > 0 Then
            allergie = tab_val_ch.Rows(0).Item("valore").ToString
        End If

        Dim testo(0) As String
        testo(0) = allergie


        Dim testo_SE As New StrucDocText
        testo_SE.Text = testo



        Dim sezione_SE As New POCD_MT000040Section
        sezione_SE.classCode = "DOCSECT"
        sezione_SE.moodCode = "EVN"
        sezione_SE.templateId = Im_Sec_Template
        sezione_SE.code = code_SE
        sezione_SE.title = titolo_SE
        sezione_SE.text = testo_SE

        Return sezione_SE
    End Function
```

3.1.2.5.5 Pharmacological therapy during hospitalization

It is an optional element that contains the list of drugs and there administration received by the patient during hospitalization.

Element <code>:

Attribute	Type	Value	Details
Code	ST	10160-0	Element extracted from the vocabulary used
codeSystem	OID	“2.16.840.1.113883.6.1”	Vocabulary OID used
codeSystemName	ST	“LOINC”	Vocabulary name used
codeSystemVersion	ST	[VERSION]	Vocabulary version used

displayName	ST	Pharmacological therapy	Name of the section or summary description of the information content according to the vocabulary used

The reletting implements is shown in the following:

```
Dim comp3_4 As New POCD_MT000040Component3
Dim Terapia_Ricovero As New POCD_MT000040Section
      Terapia_Ricovero = Crea_Terapia_Ricovero(Id_Ricovero, Id_Paziente, errstr)
      comp3_4.section = Terapia_Ricovero

Public Function Crea_Terapia_Ricovero(ByVal Id_Ricovero As String, ByVal id_paz
As String, ByRef errstr As String) As POCD_MT000040Section
      Dim Id_Templ_Sezione_TR As New II
      Id_Templ_Sezione_TR.root = "2.16.840.1.113883.2.9.10.2.99.99"
      Dim Im_Sec_Template(0) As II
      Im_Sec_Template(0) = Id_Templ_Sezione_TR

      Dim code_TR As New CE
      code_TR.code = "10160-0"
      code_TR.displayName = "Terapie Farmacologiche"
      code_TR.codeSystem = "2.16.840.1.113883.6.1"
      code_TR.codeSystemName = "LOINC"
      code_TR.codeSystemVersion = "2.19"


      Dim titolo(0) As String
      titolo(0) = "Terapia farmacologica effettuata durante il ricovero"

      Dim titolo_TR As New ST
      titolo_TR.Text = titolo

      Dim data_inizio As String = ""
      Dim inizio As DataTable = funz.dati_ricovero(Id_Ricovero, errstr)
      If inizio.Rows.Count > 0 Then
          data_inizio = inizio.Rows(0).Item("data_i").ToString
      End If
      Dim data_fine As String = ""
      Dim fine As DataTable = funz.dati_ricovero(Id_Ricovero, errstr)
      If fine.Rows.Count > 0 Then
          data_fine = fine.Rows(0).Item("data_f").ToString
      End If
      Dim giorni_ora As DataTable = funz.giorni_ora_riepilogo_terapia
      (id_paz, data_inizio, data_fine, errstr)
      Dim dettagli_terapia_tot As DataTable = funz.dettagli_terapia_fine_ricovero
      (id_paz, data_inizio, data_fine, errstr)
      Dim test(dettagli_terapia_tot.Rows.Count) As String



      For j = 0 To dettagli_terapia_tot.Rows.Count - 1
          Dim data_ann As Date = dettagli_terapia_tot.Rows(j).Item("datap")
          Dim datas4 As String
          Dim data_split4(3) As String
          data_split4 = Split(data_ann, "/")
          Dim gg As String = data_split4(0)
          Dim MM As String = data_split4(1)
          Dim anno_ora As String = data_split4(2)
          Dim anno_ora_split2(2) As String
          anno_ora_split2 = Split(anno_ora, " ")
          Dim yyyy As String = anno_ora_split2(0)
          datas4 = CDate(gg & "/" & MM & "/" & yyyy)
          Dim val As Integer = dettagli_terapia_tot.Rows(j).Item("id_orario")
          Dim ora As String = funz.dai_valore_orario(val)
```

```
        Dim pre As String
        pre = datas4 & ": " & dettagli_terapia_tot.Rows(j).Item("Farmaco").ToString
       & "   " & dettagli_terapia_tot.Rows(j).Item("dosaggio").ToString & "   " & ora

        test(j) = vbCrLf & pre & vbCrLf

    Next


    Dim testo_TR As New StrucDocText
    testo_TR.Text = test



    Dim sezione_TR As New POCD_MT000040Section
    sezione_TR.classCode = "DOCSECT"
    sezione_TR.moodCode = "EVN"
    sezione_TR.templateId = Im_Sec_Template
    sezione_TR.code = code_TR
    sezione_TR.title = titolo_TR
    sezione_TR.text = testo_TR

    Return sezione_TR
End Function
```

3.1.2.5.6 Patient condition and discharge diagnosis

This is a mandatory element that contains the patient's condition at discharge and the diagnosis in textual format and / or the list of discharge diagnoses.

Element <code>:

Attribute	Type	Value	Details
Code	ST	11535-2	Element extracted from the vocabulary used
codeSystem	OID	“2.16.840.1.113883.6.1”	Vocabulary OID used
codeSystemName	ST	“LOINC”	Vocabulary name used
codeSystemVersion	ST	[VERSION]	Vocabulary version used
displayName	ST	Patient condition and discharge diagnosis	Name of the section or summary description of the information content according to the vocabulary used

Also in this case, a title field and a text field have to be implemented. In this section is recommended to insert elements of type entry that allow you to represent in a structured way the detailed information

relating to the narrative block in a structure way. In the case of this project the entries were not inserted because the diagnosis section at discharge was designed as a free text field (therefore not coded) to come meeting the needs of hospital staff.

The function that implements this section is shown in the following:

```
Dim comp3_5 As New POCD_MT000040Component3
        Dim Diagnosi_Fine As New POCD_MT000040Section
        Diagnosi_Fine = Crea_Diagnosi_Dimissione(Id_Ricovero, errstr)
        comp3_5.section = Diagnosi_Fine

 Public Function Crea_Diagnosi_Dimissione(ByVal Id_Ricovero As String, ByRef
  errstr As String) As POCD_MT000040Section
        Dim Id_Templ_Sezione_DD As New II
        Id_Templ_Sezione_DD.root = "2.16.840.1.113883.2.9.10.2.99.99"
        Dim Im_Sec_Template(0) As II
        Im_Sec_Template(0) = Id_Templ_Sezione_DD

        Dim code_DD As New CE
        code_DD.code = "11535-2"
        code_DD.displayName = "Diagnosi di Dimissione"
        code_DD.codeSystem = "2.16.840.1.113883.6.1"
        code_DD.codeSystemName = "LOINC"
        code_DD.codeSystemVersion = "2.19"


        Dim titolo(0) As String
        titolo(0) = "Condizioni del paziente e diagnosi alla dimissione"

        Dim titolo_DD As New ST
        titolo_DD.Text = titolo
        Dim par_dia As String = "Diagnosi di Fine Ricovero"
        Dim id_dia As Integer = funz.dai_id_par_da_nome(par_dia)
        Dim tab_3 As DataTable = funz.dai_valori_CHAR_per_modifica_accettazione
        (Id_Ricovero, id_dia, errstr)
        Dim diagnosi As String = ""
        If tab_3.Rows.Count > 0 Then
            diagnosi = tab_3.Rows(0).Item("valore").ToString
        End If

        Dim testo(0) As String
        testo(0) = diagnosi


        Dim testo_DD As New StrucDocText
        testo_DD.Text = testo




        Dim sezione_DD As New POCD_MT000040Section
        sezione_DD.classCode = "DOCSECT"
        sezione_DD.moodCode = "EVN"
        sezione_DD.templateId = Im_Sec_Template
        sezione_DD.code = code_DD
        sezione_DD.title = titolo_DD
        sezione_DD.text = testo_DD

        Return sezione_DD
    End Function
```

3.1.2.5.7 Pharmacological therapy at discharge

It is an optional element that contains the list of drugs that the patient should take at home.

The <code> element is as follows:

Attribute	Type	Value	Details
Code	ST	10183-2	Element extracted from the vocabulary used
codeSystem	OID	"2.16.840.1.113883.6.1"	Vocabulary OID used
codeSystemName	ST	"LOINC"	Vocabulary name used
codeSystemVersion	ST	[VERSION]	Vocabulary version used
displayName	ST	Pharmacological therapy at discharge	Name of the section or summary description of the information content according to the vocabulary used

Function:

```
Dim comp3_7 As New POCD_MT000040Component3
        Dim ter_dimissione As New POCD_MT000040Section
        ter_dimissione = Crea_Terapia_Dimissione(Id_Ricovero, Id_Paziente, errstr)
        comp3_7.section = ter_dimissione

    Public Function Crea_Terapia_Dimissione(ByVal Id_Ricovero As String, ByVal
    id_paz As String, ByRef errstr As String) As POCD_MT000040Section
        Dim Id_Templ_Sezione_TD As New II
        Id_Templ_Sezione_TD.root = "2.16.840.1.113883.2.9.10.2.99.99"
        Dim Im_Sec_Template(0) As II
        Im_Sec_Template(0) = Id_Templ_Sezione_TD

        Dim code_TD As New CE
        code_TD.code = "10183-2"
        code_TD.displayName = "Terapie Farmacologiche"
        code_TD.codeSystem = "2.16.840.1.113883.6.1"
        code_TD.codeSystemName = "LOINC"
        code_TD.codeSystemVersion = "2.19"


        Dim titolo(0) As String
        titolo(0) = "Terapia farmacologica alla dimissione"

        Dim titolo_TD As New ST
        titolo_TD.Text = titolo

        Dim data_inizio As String = ""
        Dim inizio As DataTable = funz.dati_ricovero(Id_Ricovero, errstr)
        If inizio.Rows.Count > 0 Then
```

```
            data_inizio = inizio.Rows(0).Item("data_i").ToString
        End If
        Dim data_fine As String = ""
        Dim fine As DataTable = funz.dati_ricovero(Id_Ricovero, errstr)
        If fine.Rows.Count > 0 Then
            data_fine = fine.Rows(0).Item("data_f").ToString
        End If
        Dim giorni_ora As DataTable = funz.giorni_ora_riepilogo_terapia(id_paz,
        data_inizio, data_fine, errstr)
        Dim dettagli_terapia_tot As DataTable = funz.dettagli_terapia_fine_ricovero
        (id_paz, data_inizio, data_fine, errstr)
        Dim test(dettagli_terapia_tot.Rows.Count) As String


        For j = 0 To dettagli_terapia_tot.Rows.Count - 1
            Dim data_ann As Date = dettagli_terapia_tot.Rows(j).Item("datap")
            If data_ann = data_fine Then
                Dim val As Integer = dettagli_terapia_tot.Rows(j).Item("id_orario")
                Dim ora As String = funz.dai_valore_orario(val)
                Dim pre As String
                pre = dettagli_terapia_tot.Rows(j).Item("Farmaco").ToString & "   " &
                dettagli_terapia_tot.Rows(j).Item("dosaggio").ToString & "   " & ora
                test(j) = vbCrLf & pre & vbCrLf
            End If
        Next


        Dim testo_TD As New StrucDocText
        testo_TD.Text = test



        Dim sezione_TD As New POCD_MT000040Section
        sezione_TD.classCode = "DOCSECT"
        sezione_TD.moodCode = "EVN"
        sezione_TD.templateId = Im_Sec_Template
        sezione_TD.code = code_TD
        sezione_TD.title = titolo_TD
        sezione_TD.text = testo_TD

        Return sezione_TD
    End Function
```

3.1.2.5.8 Follow-up Instructions

It is an optional element that provides general information relating to the clinical event for the transition of care from the hospital to the territorial context. In this section any checks, procedures or recommended visits may be described.

The <code> element is as follows:

Attribute	Type	Value	Details

Code	ST	18776-5	Element extracted from the vocabulary used
codeSystem	OID	“2.16.840.1.113883.6.1”	Vocabulary OID used

codeSystemName	ST	“LOINC”	Vocabulary name used
codeSystemVersion	ST	[VERSION]	Vocabulary version Used
displayName	ST	Care Plan	Name of the section or summary description of the information content according to the vocabulary used

Function:

```
Dim comp3_6 As New POCD_MT000040Component3
      Dim Raccomandazioni As New POCD_MT000040Section
      Raccomandazioni = Crea_Istruzioni(Id_Ricovero, errstr)
      comp3_6.section = Raccomandazioni

Public Function Crea_Istruzioni(ByVal Id_Ricovero As String, ByRef errstr As String)
As POCD_MT000040Section
      Dim Id_Templ_Sezione_IF As New II
      Id_Templ_Sezione_IF.root = "2.16.840.1.113883.2.9.10.2.99.99"
      Dim Im_Sec_Template(0) As II
      Im_Sec_Template(0) = Id_Templ_Sezione_IF

      Dim code_IF As New CE
      code_IF.code = "18776-5"
      code_IF.displayName = "Piano di Cura"
      code_IF.codeSystem = "2.16.840.1.113883.6.1"
      code_IF.codeSystemName = "LOINC"
      code_IF.codeSystemVersion = "2.19"


      Dim titolo(0) As String
      titolo(0) = "Istruzioni di follow-up"

      Dim titolo_IF As New ST
      titolo_IF.Text = titolo
      Dim par_racc As String = "Raccomandazioni"
      Dim id_racc As Integer = funz.dai_id_par_da_nome(par_racc)
      Dim raccomandazioni As String = ""
      Dim tab_4 As DataTable = funz.dai_valori_CHAR_per_modifica_accettazione
      (Id_Ricovero, id_racc, errstr)
      If tab_4.Rows.Count > 0 Then
          raccomandazioni = tab_4.Rows(0).Item("valore").ToString
      End If

      Dim testo(0) As String
      testo(0) = raccomandazioni


      Dim testo_IF As New StrucDocText
      testo_IF.Text = testo



      Dim sezione_IF As New POCD_MT000040Section
      sezione_IF.classCode = "DOCSECT"
      sezione_IF.moodCode = "EVN"
```

```
       sezione_IF.templateId = Im_Sec_Template
       sezione_IF.code = code_IF
       sezione_IF.title = titolo_IF
       sezione_IF.text = testo_IF

       Return sezione_IF
   End Function
```

The code that implements the full body, calling le functions already described is as follows:

```
Dim component2 As New POCD_MT000040Component2
Dim structuredBody As New POCD_MT000040StructuredBody
Dim comp3 As New POCD_MT000040Component3
Dim Motivo_Ricovero As New POCD_MT000040Section
Motivo_Ricovero = Crea_Motivo_ricovero(Id_Ricovero, errstr)
comp3.section = Motivo_Ricovero
Dim comp3_4 As New POCD_MT000040Component3
Dim Terapia_Ricovero As New POCD_MT000040Section
Terapia_Ricovero = Crea_Terapia_Ricovero(Id_Ricovero, Id_Paziente, errstr)
comp3_4.section = Terapia_Ricovero
Dim comp3_6 As New POCD_MT000040Component3
Dim Raccomandazioni As New POCD_MT000040Section
Raccomandazioni = Crea_Istruzioni(Id_Ricovero, errstr)
comp3_6.section = Raccomandazioni
Dim comp3_7 As New POCD_MT000040Component3
Dim ter_dimissione As New POCD_MT000040Section
ter_dimissione = Crea_Terapia_Dimissione(Id_Ricovero, Id_Paziente, errstr)
comp3_7.section = ter_dimissione
Dim comp3_5 As New POCD_MT000040Component3
Dim Diagnosi_Fine As New POCD_MT000040Section
Diagnosi_Fine = Crea_Diagnosi_Dimissione(Id_Ricovero, errstr)
comp3_5.section = Diagnosi_Fine
Dim comp3_3 As New POCD_MT000040Component3
Dim Allergie As New POCD_MT000040Section
Allergie = Crea_Sezione_Allergie(Id_Ricovero, errstr)
comp3_3.section = Allergie
Dim comp3_2 As New POCD_MT000040Component3
Dim Decorso_Ospedaliero As New POCD_MT000040Section
Decorso_Ospedaliero = Crea_Decorso_Ospedaliero(Id_Ricovero, errstr)
comp3_2.section = Decorso_Ospedaliero
Dim comp3_1 As New POCD_MT000040Component3
Dim ICI As New POCD_MT000040Section
ICI = Crea_Inquadramento_Clinico_Iniziale(Id_Ricovero, errstr)
comp3_1.section = ICI
Dim component3(7) As POCD_MT000040Component3
component3(0) = comp3
component3(0).typeCode = ActRelationshipHasComponent.COMP
component3(0).contextConductionInd = True
component3(1) = comp3_1
component3(1).typeCode = ActRelationshipHasComponent.COMP
component3(1).contextConductionInd = True
component3(2) = comp3_2
component3(2).typeCode = ActRelationshipHasComponent.COMP
component3(2).contextConductionInd = True
component3(3) = comp3_3
component3(3).typeCode = ActRelationshipHasComponent.COMP
component3(3).contextConductionInd = True
component3(4) = comp3_4
component3(4).typeCode = ActRelationshipHasComponent.COMP
component3(4).contextConductionInd = True
component3(5) = comp3_5
component3(5).typeCode = ActRelationshipHasComponent.COMP
component3(5).contextConductionInd = True
```

```
component3(6) = comp3_7
component3(6).typeCode = ActRelationshipHasComponent.COMP
component3(6).contextConductionInd = True
component3(7) = comp3_6
component3(7).typeCode = ActRelationshipHasComponent.COMP
component3(7).contextConductionInd = True
structuredBody.classCode = "DOCBODY"
structuredBody.moodCode = "EVN"
structuredBody.component = component3

component2.typeCode = ActRelationshipHasComponent.COMP
component2.contextConductionInd = True
component2.Item = structuredBody
```

The implementation of the CDA (Create_CDA () function) will therefore be structured as follows:

```
Dim CDA As New POCD_MT000040ClinicalDocument
CDA.classCode = ActClinicalDocument.DOCCLIN
CDA.moodCode = "EVN"
CDA.realmCode = Header_realmCode
CDA.typeId = Header_TypeId
CDA.templateId = H_templ
CDA.id = Header_Id_CDA
CDA.code = Header_Code
CDA.title = Header_Title
CDA.effectiveTime = Header_EffectiveTime
CDA.confidentialityCode = Header_ConfidentialityCode
CDA.languageCode = Header_LanguageCode
CDA.versionNumber = Header_versionNumber
CDA.setId = Heder_SetId
CDA.recordTarget = Header_RecordTarget
CDA.author = Header_Author
CDA.custodian = Header_Custodian
CDA.legalAuthenticator = Header_LegalAuthenticator
CDA.componentOf = Header_componentOf
CDA.component = component2

Return CDA
```

For each element, the code that implements it has already been described.

An example of the generated CDA.xml is shown below.

```
<?xml version="1.0" encoding="utf-8"?>
<ClinicalDocument xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance"
 xmlns:xsd="http://www.w3.org/2001/XMLSchema" moodCode="EVN" xmlns="urn:hl7-org:v3">
  <realmCode code="IT" />
  <typeId root="2.16.840.1.113883.1.3" extension="POCD_HD000040" />
  <templateId root="2.16.840.1.113883.2.9.10.1.5" />
  <id root="2.16.840.1.113883.2.9.2.07030104" extension="LDO_2017700134"
  assigningAuthorityName="ASL 3 VILLA SCASSI" />
  <code code="34105-7" codeSystem="2.16.840.1.113883.6.1" codeSystemName="LOINC"
  codeSystemVersion="2.19" displayName="Lettera di dimissione ospedaliera" />
  <title>Lettera di dimissione ospedaliera</title>
  <effectiveTime value="20170316130038+0100" />
  <confidentialityCode code="N" codeSystem="2.16.840.1.113883.5.25" codeSystemName="Confidentiality"
  displayName="Normale" />
  <languageCode code="it-IT" />
  <setId root="2.16.840.1.113883.2.9.2.07030104.4.4" extension="Id_Ricovero"
  assigningAuthorityName="ASL 3 VILLA SCASSI" />
  <versionNumber value="1" />
  <recordTarget typeCode="RCT" contextControlCode="OP">
    <patientRole classCode="PAT">
      <id root="2.16.840.1.113883.2.9.4.3.2" extension="DFTQXP74R22K296T"
      assigningAuthorityName="Ministero Economia e Finanze" />
```

```
    <patient classCode="PSN" determinerCode="INSTANCE">
      <name>
        <given>Lucia</given>
        <family>Rossi</family>
      </name>
      <administrativeGenderCode code="F" codeSystem="2.16.840.1.113883.5.1" />
      <birthTime value="19560422" />
    </patient>
  </patientRole>
</recordTarget>
<author typeCode="AUT" contextControlCode="OP">
  <time value="20170316130038+0100" />
  <assignedAuthor classCode="ASSIGNED">
    <id root="2.16.840.1.113883.2.9.4.3.2" extension="dfrlvt125dertubd" />
  </assignedAuthor>
</author>
<custodian typeCode="CST">
  <assignedCustodian classCode="ASSIGNED">
    <representedCustodianOrganization classCode="ORG" determinerCode="INSTANCE">
      <id root="2.16.840.1.113883.2.9.4.1.2" extension="07030104" />
      <name>ASL 3 Ospedale Villa Scassi</name>
    </representedCustodianOrganization>
  </assignedCustodian>
</custodian>
<legalAuthenticator typeCode="LA" contextControlCode="OP">
  <time nullFlavor="NAV" value="20170316130038+0100" />
  <signatureCode code="S" />
  <assignedEntity classCode="ASSIGNED">
    <id root="2.16.840.1.113883.2.9.4.3.2" extension="dfrlvt125dertubd" />
  </assignedEntity>
</legalAuthenticator>
<componentOf>
  <encompassingEncounter classCode="ENC" moodCode="EVN">
    <id root="2.16.840.1.113883.2.9.2.07030104.4.6" extension="2017700134"
    assigningAuthorityName="ASL 3 Villa Scassi" />
    <effectiveTime>
      <low value="20170314000000+0100" />
      <high value="20170314000000+0100" />
    </effectiveTime>
    <location>
      <healthCareFacility>
        <id root="2.16.840.1.113883.2.9.4.1.6" extension="070301.04.08" />
        <location determinerCode="INSTANCE">
          <name>Reparto di cardiologia</name>
        </location>
        <serviceProviderOrganization classCode="ORG" determinerCode="INSTANCE">
          <id root="2.16.840.1.113883.2.9.4.1.2" extension="07030104"
          assigningAuthorityName="MINISTERO DELLA SALUTE" />
         </serviceProviderOrganization>
      </healthCareFacility>
    </location>
  </encompassingEncounter>
</componentOf>
<component>
  <structuredBody classCode="DOCBODY" moodCode="EVN">
    <component>
      <section classCode="DOCSECT" moodCode="EVN">
        <templateId root="2.16.840.1.113883.2.9.10.2.99.99" />
        <code code="46241-6" codeSystem="2.16.840.1.113883.6.1" codeSystemName="LOINC"
        codeSystemVersion="2.19" displayName="Diagnosi di Accettazione" />
        <title>Motivo del Ricovero</title>
        <text>
        sindrome coronarica acuta in cardiopatia ischemica
        </text>
      </section>
    </component>
    <component>
```

```
      <section classCode="DOCSECT" moodCode="EVN">
        <templateId root="2.16.840.1.113883.2.9.10.2.99.99" />
        <code code="47039-3" codeSystem="2.16.840.1.113883.6.1" codeSystemName="LOINC"
        codeSystemVersion="2.19" displayName="Ricovero Ospedaliero, anamnesi ed esame obiettivo" />
        <title>Inquadramento Clinico Iniziale</title>
        <text>
        Dislipidemia: Non nota.
        Familiarità: Si.
        Fumo: Ex.
        Ipertensione: No.
        Diabete: No.
        </text>
        <component>
          <section classCode="DOCSECT" moodCode="EVN">
            <templateId root="2.16.840.1.113883.2.9.10.2.99.99" />
            <code code="11329-0" codeSystem="2.16.840.1.113883.6.1" codeSystemName="LOINC"
            codeSystemVersion="2.19" displayName="Anamnesi Generale" />
            <title>Anamnesi Generale</title>
            <text>
              Anamnesi Recente: Durante l'anno 2004 accusava problemi respiratori che intensificavano
              con l'abbassarsi della temperatura atmosferica.
              Nonostante la vaccinazione anti-influenzale, è stata colpita da sindrome influenzale
              Anamnesi Remota: Nell'anno 1988 ha subito appendicectomia.
              Nell'anno 1999 intervento per spina ossea all'arcata dentale superiore.
              Nell'anno 2002 Angioplastica PTCA + Stent
            </text>
          </section>
        </component>
        <component>
          <section classCode="DOCSECT" moodCode="EVN">
            <templateId root="2.16.840.1.113883.2.9.10.2.99.99" />
            <code code="29545-1" codeSystem="2.16.840.1.113883.6.1" codeSystemName="LOINC"
            codeSystemVersion="2.19" displayName="Esame Obiettivo" />
            <title>Esame Obiettivo</title>
            <text>
            Generale: Edemi Malleolari; Decubito Indifferente; Cute Calda e asciutta;
            Sensorio Vigile, orientato.
            Addome: Palpazione Trattabile, non dolente, nè dolorabile; Fegato Nei limiti
            Torace: Ispezione e palpazione Nella norma; Percussione SCP su tutto l'ambito;
            Ascoltazione torace MV su tutto l'ambito
            Apparato Cardiovascolare: Pressione 110/60 mmHg; Frequenza cardiaca 100 bpm;
            Ascoltazione Toni Toni ridotti di intensità; Ascoltazione Soffi Non soffi patologici;
            Polsi Periferici Eusfigmici
            </text>
          </section>
        </component>
        <component>
          <section classCode="DOCSECT" moodCode="EVN">
            <templateId root="2.16.840.1.113883.2.9.10.2.99.99" />
            <code code="42346-7" codeSystem="2.16.840.1.113883.6.1" codeSystemName="LOINC"
            codeSystemVersion="2.19" displayName="Terapia Farmacologica allâ€™ingresso" />
            <title>Terapia Farmacologica allâ€™Ingresso</title>
            <text>
             Nessuna
            </text>
          </section>
        </component>
      </section>
    </component>
    <component>
      <section classCode="DOCSECT" moodCode="EVN">
        <templateId root="2.16.840.1.113883.2.9.10.2.99.99" />
        <code code="8648-8" codeSystem="2.16.840.1.113883.6.1" codeSystemName="LOINC"
        codeSystemVersion="2.19" displayName="Decorso ospedaliero" />
        <title>Decorso Ospedaliero</title>
        <text>
          14/03/2017  14:00:00  E' stata eseguita una valutazione ecocardiografica della malattia
```

```
                              valvolare aortica

          15/03/2017  18:00:00  correzione della stenosi valvolare mediante impianto di protesi
                              valvolare

          16/03/2017  16:00:00  il paziente presenta segni di miglioramento
        </text>
      </section>
    </component>
    <component>
      <section classCode="DOCSECT" moodCode="EVN">
        <templateId root="2.16.840.1.113883.2.9.10.2.99.99" />
        <code code="48765-2" codeSystem="2.16.840.1.113883.6.1" codeSystemName="LOINC"
        codeSystemVersion="2.19" displayName="ALLERGIE E/O REAZIONI AVVERSE" />
        <title>Allergie e/o Reazioni Avverse</title>
        <text>cortisone </text>
      </section>
    </component>
    <component>
      <section classCode="DOCSECT" moodCode="EVN">
        <templateId root="2.16.840.1.113883.2.9.10.2.99.99" />
        <code code="10160-0" codeSystem="2.16.840.1.113883.6.1" codeSystemName="LOINC"
        codeSystemVersion="2.19" displayName="Terapie Farmacologiche" />
        <title>Terapia farmacologica effettuata durante il ricovero</title>
        <text>
          14/03/2017: ACIDO ACETILSALICILICO SANDOZ  100 MG   2 CPR  18:00:00

          14/03/2017: ACIDO ACETILSALICILICO SANDOZ  100 MG   2 CPR  22:00:00

          16/03/2017: CLARITROL  500 MG   3 CPR  20:00:00

          16/03/2017: ACIDO ACETILSALICILICO EG  100 MG   2 CPR  16:00:00
        </text>
      </section>
    </component>
    <component>
      <section classCode="DOCSECT" moodCode="EVN">
        <templateId root="2.16.840.1.113883.2.9.10.2.99.99" />
        <code code="11535-2" codeSystem="2.16.840.1.113883.6.1" codeSystemName="LOINC"
        codeSystemVersion="2.19" displayName="Diagnosi di Dimissione" />
        <title>Condizioni del paziente e diagnosi alla dimissione</title>
        <text>
          insufficienza della valvola aortica di grado severo
        </text>
      </section>
    </component>
    <component>
      <section classCode="DOCSECT" moodCode="EVN">
        <templateId root="2.16.840.1.113883.2.9.10.2.99.99" />
        <code code="10183-2" codeSystem="2.16.840.1.113883.6.1" codeSystemName="LOINC"
        codeSystemVersion="2.19" displayName="Terapie Farmacologiche" />
        <title>Terapia farmacologica alla dimissione</title>
        <text>
          CLARITROL  500 MG   3 CPR  20:00:00

          ACIDO ACETILSALICILICO EG  100 MG   2 CPR  16:00:00
        </text>
      </section>
    </component>
    <component>
      <section classCode="DOCSECT" moodCode="EVN">
        <templateId root="2.16.840.1.113883.2.9.10.2.99.99" />
        <code code="18776-5" codeSystem="2.16.840.1.113883.6.1" codeSystemName="LOINC"
        codeSystemVersion="2.19" displayName="Piano di Cura" />
        <title>Istruzioni di follow-up</title>
        <text>
          viene data indicazione a correzione della stenosi valvolare mediante impianto di
```

```
            protesi valvolare per via percutanea
          </text>
        </section>
      </component>
    </structuredBody>
  </component>
</ClinicalDocument>
```

All the OIDs in the CDA implemented have been built according to the schemes for the construction of the same ones mentioned previously. These OIDs have been proposed and are awaiting approval by HL7 Italy.

3.1.3. Description of the decision support tools

During the routine use of the EHRS, the physicians requested support for some procedures that could be improved using specific AI algorithms.

The knowledge required for these algorithms has been obtained from direct interaction with physicians of the wards and from cardiology guidelines [30], [65], [67], [68]. For the management of these guidelines, we used the GLIF, which is a language for the structured representation of clinical guidelines. The GLIF editor, developed by Medical Objects, has been used to draw the logical flux used in these decision support tools with the contributions by the physicians of the ward. Patients' states, decisions, actions, and the related links have been also described in a computer interpretable way using the GLIF editor. To embed automatic decision steps, scripts in the GELLO language [67] have been used. Moreover, generalized data, extracted by grouping procedures within the real CEHRS database, have been used to set up a VMR for each patient.

The main decision support tools that have been developed are shown in the following.

For FH patients with ASCVD who are at very-high risk, treatment to achieve a ≥50% reduction from baseline and an LDL-C <1.4 mmol/L (<55 mg/dL) is recommended. If goals cannot be achieved, a drug combination is recommended.	I	C
Treatment with a PCSK9 inhibitor is recommended in very-high risk FH patients if the treatment goal is not achieved on a maximal tolerated statin plus ezetimibe.	I	C
In children, testing for FH is recommended from the age of 5 years, or earlier if HoFH is suspected.	I	C
Treatment of dyslipidaemias in older people		
Treatment with statins is recommended for older people with ASCVD in the same way as for younger patients.	I	A
Treatment with statins is recommended for primary prevention, according to the level of risk, in older people aged ≤75 years.	I	A
It is recommended that the statin is started at a low dose if there is significant renal impairment and/or the potential for drug interactions, and then titrated upwards to achieve LDL-C treatment goals.	I	C
Treatment of dyslipidaemias in DM		
In patients with T2DM at very-high risk,[c] an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) is recommended.	I	A
In patients with T2DM at high risk,[c] an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) is recommended.	I	A
Statins are recommended in patients with T1DM who are at high or very-high risk.[c]	I	A
Statin therapy is not recommended in pre-menopausal patients with or without DM who are considering pregnancy, or not using adequate contraception.	III	C
Management of patients with ACS		
In all ACS patients without any contraindication or definite history of intolerance, it is recommended that high-dose statin therapy is initiated or continued as early as possible, regardless of initial LDL-C values.	I	A
If the LDL-C goal is not achieved after 4–6 weeks with the maximally tolerated statin dose, combination with ezetimibe is recommended.	I	B
If the LDL-C goal is not achieved after 4–6 weeks despite maximal tolerated statin therapy and ezetimibe, adding a PCSK9 inhibitor is recommended.	I	B
Lipid-lowering therapy for prevention of ASCVD events in patients with prior ischaemic stroke		
Patients with a history of ischaemic stroke or TIA are at very-high risk of ASCVD, particularly recurrent ischaemic stroke, so it is recommended that they receive intensive LDL-C-lowering therapy.	I	A
Treatment of dyslipidaemias in chronic HF or valvular heart diseases		
Initiation of lipid-lowering therapy is not recommended in patients with HF in the absence of other indications for their use.	III	A
Initiation of lipid-lowering treatment is not recommended in patients with aortic valvular stenosis without CAD to slow progression of aortic valve stenosis in the absence of other indications for their use.	III	A
Lipid management in patients with moderate-to-severe (Kidney Disease Outcomes Quality Initiative stages 3–5) CKD		
It is recommended that patients with stage 3–5 CKD are considered to be at high or very-high risk of ASCVD.	I	A
The use of statins or statin/ezetimibe combination is recommended in patients with non-dialysis-dependent stage 3–5 CKD.	I	A
In patients with dialysis-dependent CKD who are free of ASCVD, commencement of statin therapy is not recommended.	III	A
Lipid-lowering drugs in patients with PAD (including carotid artery disease)		
In patients with PAD, lipid-lowering therapy—including a maximum tolerated dose of a statin, plus ezetimibe, or a combination with a PCSK9 inhibitor if needed—is recommended to reduce the risk of ASCVD events.	I	A
Lipid-lowering drugs in patients with CIID		
The use of lipid-lowering drugs only on the basis of the presence of CIID is not recommended.	III	C
Lipid-lowering drugs in patients with SMI		
It is recommended that SMIs are used as modifiers for estimating total ASCVD risk.	I	C
It is recommended that the same guidelines for the management of total ASCVD risk are used in patients with SMI as are used in patients without such disease.	I	C
It is recommended that in patients with SMI, intensified attention is paid to adherence to lifestyle changes and to compliance with drug treatment.	I	C

ACS = acute coronary syndrome(s); Apo = apolipoprotein; ASCVD = atherosclerotic cardiovascular disease; CAD = coronary artery disease; CHD = coronary heart disease; CIID = chronic immune-mediated inflammatory diseases; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; FH = familial hypercholesterolaemia; HDL-C = high-density lipoprotein cholesterol; HeFH = heterozygous FH; HF = heart failure; HoFH = homozygous FH; HTG = hypertriglyceridaemia; LDL-C = low-density lipoprotein cholesterol; MetS = metabolic syndrome; PAD = peripheral arterial disease; PCSK9 = proprotein convertase subtilisin/kexin type 9; SCORE = Systematic Coronary Risk Estimation; SMI = severe mental illness; TC = total cholesterol; TG = triglycerides; TIA = transient ischaemic event; T1DM = type 1 DM; T2DM = type 2 DM.

[a]Class of recommendation.

[b]Level of evidence.

Figure 3.14 Guide Lines example [[69]]

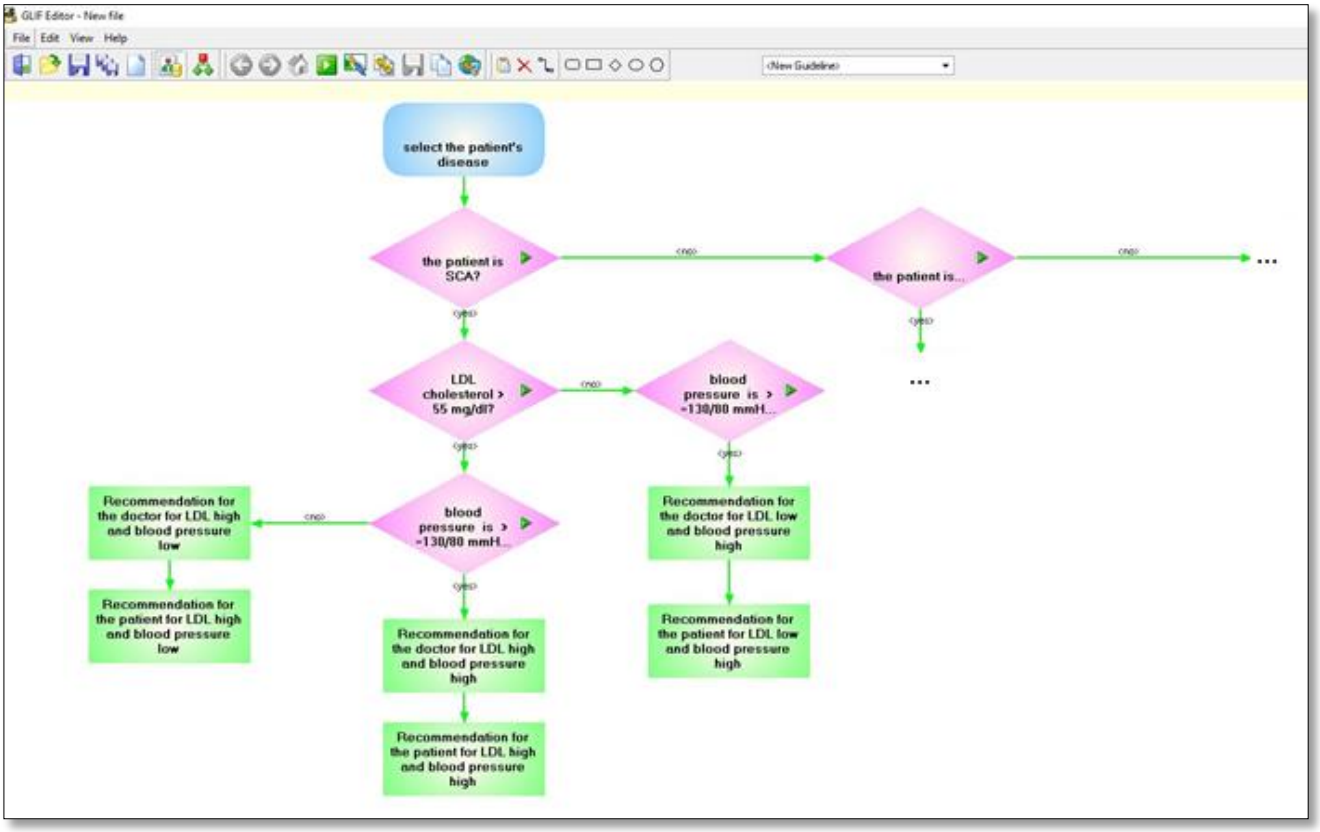

Figure 3.15. Definition of recommendations for doctors based on the value of LDL cholesterol and the value of blood in different types of heart patients developed with GLIF Editor of Medical Objects

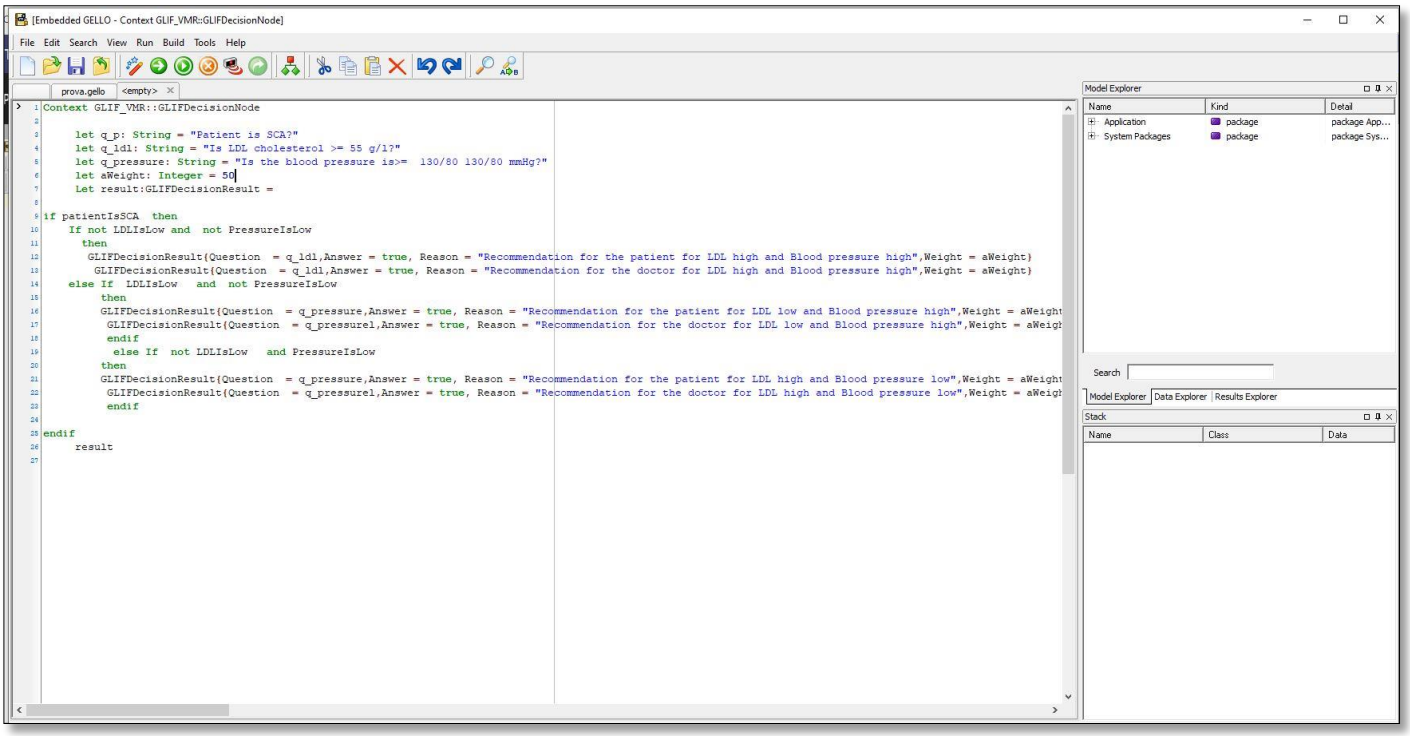

Figure 3.16: GELLO code execution in GLIF decision node. The GELLO code related to the first decision step evaluates if the last value of LDL cholesterol of the patient considered is lower than the set threshold (55 mL/min). LOINC code is used to identify the parameter.

3.1.3.1. Therapy administration

The oxygen and infusion therapy administrations are supported by a rule-based algorithm. Specifically, for the oxygen therapy, when a complex mask is needed (for example the Ventu Mask [68]), the physician has to define a minimum set of fundamental parameters (for example, the fraction of oxygen in the inspired gas mixture and the positive end-expiratory pressure) and all other parameters are calculated from the patient parameters according to clinical guidelines. Similarly, for the infusion therapy, the physician has to select the drug, to define its amount and the delivery rate. All other parameters (concentration, velocity, end of treatment time, etc.) are calculated from the patients' features extracted from the personalized VMR interpreted according to GELLO structured guidelines.

3.1.3.2. HDLET Drafting

The HDLET is a key document for the follow-up of the patient after hospitalization, but in many cases it suffers due to the limited time that can be devoted to it. The highly de-tailed analytical structure of the data stored in the CEHRS allows for an in-depth analysis of the data collected during hospitalization. The results of this analysis are transmitted to a rule-based algorithm, which precompiles some free text areas of the HDLET using an ensemble of pre-defined sentences that are suitable for the features of the patient. The physician has to read, modify if necessary and confirm acceptance. Acceptance by the physician implies his/her taking responsibility, confirmed by his/her digital signature. The HDLET management process continues as described in paragraph 3.1.2.4.

3.1.4. Emergency System

An emergency system has been developed to overcome the servers' failures. The system's architecture is shown in Figure 3.17.

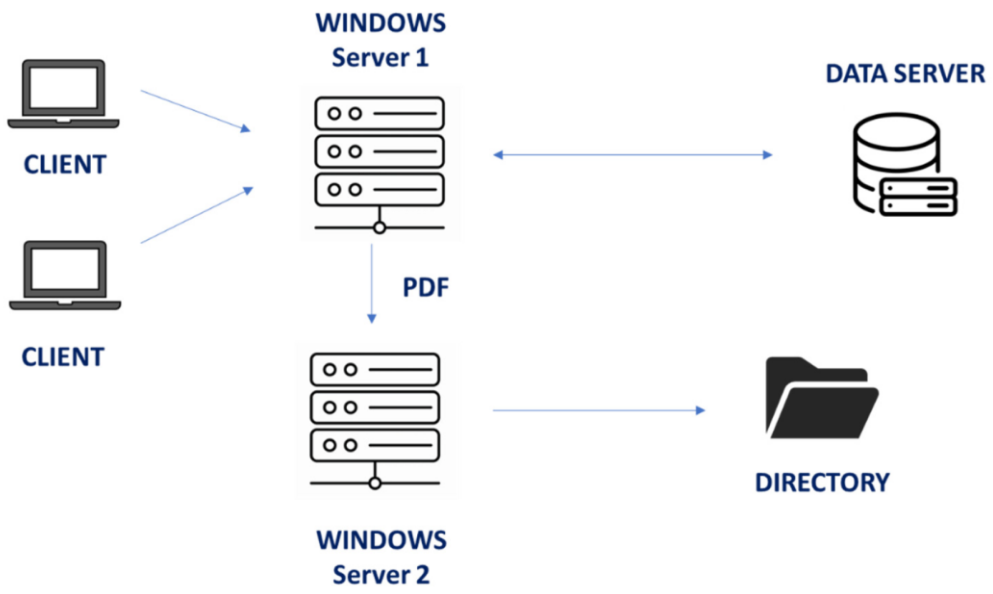

Figure 3.17. Architecture of the CEHRS emergency system.

The Windows Server 1, which is the main server in which the CEHRS is located, is connected with the data server, with the clients and with another server.

During normal operations Server 1 stores the state of the clinical record of each patient as a PDF file in a directory that is shared by a web interface, which is managed by Server 2. The files are updated every four hours. If a Server 1 malfunction occurs, users can use the shared files in the directory, which resides in Server 2.

This architecture has been chosen in order to duplicate the hardware and, therefore, halve the probability to have both servers out of service at the same time. Moreover, Server 2 includes all the necessary resources and, therefore, does not need any connection in or-der to properly function. This makes it more robust than Server 1.

3.1.5. Practical implications of the system

An informal survey that has been conducted in the two hospitals. After one month routine use of the EHR at the and of each working shift, I have personally interviewed both medical and nursing staff about acceptance and liking of the EHR. In VS hospital 15 medical doctors and 30 nurses were interviewed, and in AM hospital 12 medical doctors and 25 nurses were interviewed. Using EHRs has improved patient management according to 75% of physicians and 60% of nurses in VS hospital, and according to 65% of physicians and 45% of nurses in PAM hospital. It is thought that the difference between the two hospitals is probably due to the fact that in PAM hospital, the use of the EHR is more recent; therefore, the lower satisfaction is a consequence of the fact that familiarity with EHR is still rather low. For both hospitals, the tool that was mostly appreciated by physicians

was the software supporting the HDLET preparation (90% in VS hospital, 75% in PAM hospital). Further surveys will be proposed in the future to check the satisfaction trend.

A further aspect that has been regarded as very useful by physicians is sharing data between the two hospitals, which significantly reduces anamnesis time when the same patient is admitted at different times in the two hospitals (90% in VS hospital, 75% in PAM hospital).

Nurses especially appreciated the possibility of quickly recording missed therapy administrations and its causes (75% in VS hospital, 60% in PAM hospital).

3.2 Supporting clinical trials on mortality prediction in patients with heart failure by a standard-based EHR

3.2.1 Inclusion criteria

Villa Scassi is one of the main hospitals in Genoa (Italy) and each year its cardiological ward hosts more than 1000 patients suffering from different cardiac diseases. Among them, we selected heart failure patients with primary diagnosis of “Heart Failure” (ICD-9 code 428) hospitalized between 2019-2021 and who performed at least one laboratory test during the hospitalization. This is an anonymous, retrospective, observational study that complies with the principles outlined in the Declaration of Helsinki. All participants gave informed consent for data collection and usage for scientific purposes.

3.2.2 Sample features

● **Samples**: Each patient contributes with only one hospitalization. According to the indications of clinicians, hospitalizations that occur in a time span of less than 30 days have been merged in one event, while for longer time spans the event that lasted more days and/or the one with a more complete set of data was considered. The sample is composed of 180 patients with the same number of hospitalizations.

● **Features:** The dataset includes 4 broad classes of features (N = 197):
○ Demographic features: age and sex.
○ Anamnestic features: diabetes, smoking and hypertension.
○ Therapeutic features: Angiotensin-Converting Enzyme (ACE) inhibitors, heparins and sartanics.
○ Ecographic features: ejection fraction(EF) and VS- teleDiastolic diameter.
○ Laboratory features: results of laboratory exams done during hospitalization

● **Labels:** target class “1” represents patients deceased within 6 months from the hospitalization (N = 84) while class “0” represents patients not deceased (N = 96). As Table 1 shows

deceased patients were predominantly males (61,7%) and 84% of them were older than 65.
The dataset is balanced- data balancing is essential to have accurate results.

	HF patients non deceased (*n* = 96)	HF patients deceased(*n* = 84)	*p*-Value
Variable, median (Q1–Q3)]			
Age, years	77.0 (66.8, 84.0)	81.5 (73.0, 87.0)	0.005
Ejection Fraction	40.0 (28.0, 51.0)	41.5 (28.0, 55.0)	0.853
VS - TeleDiastolic Diameter	55.5 (48.3, 62.0)	52.0 (46.0, 62.0)	0.563
Variable, *n* (%)			
Gender, males	55.0 (57.3)	56.0 (66.7)	0.256
Diabetes	21.0 (26.3)	38.0 (57.6)	< 0.001
Hypertension	69.0 (76.6)	66.0 (85.7)	0.199
Smoke	24.0 (32.9)	19.0 (30.6)	0.927
GFR	89 (92.7)	71 (84.5)	0.132
ACEI	69.0 (71.9)	38.0 (46.9)	0.001
Heparinics	34.0 (35.4)	42.0 (51.9)	0.041
Sartanics	13.0 (13.5)	10.0 (12.3)	0.991

Figure 3.17 Statistical analysis for each class

3.2.3 Data Extraction and Storage

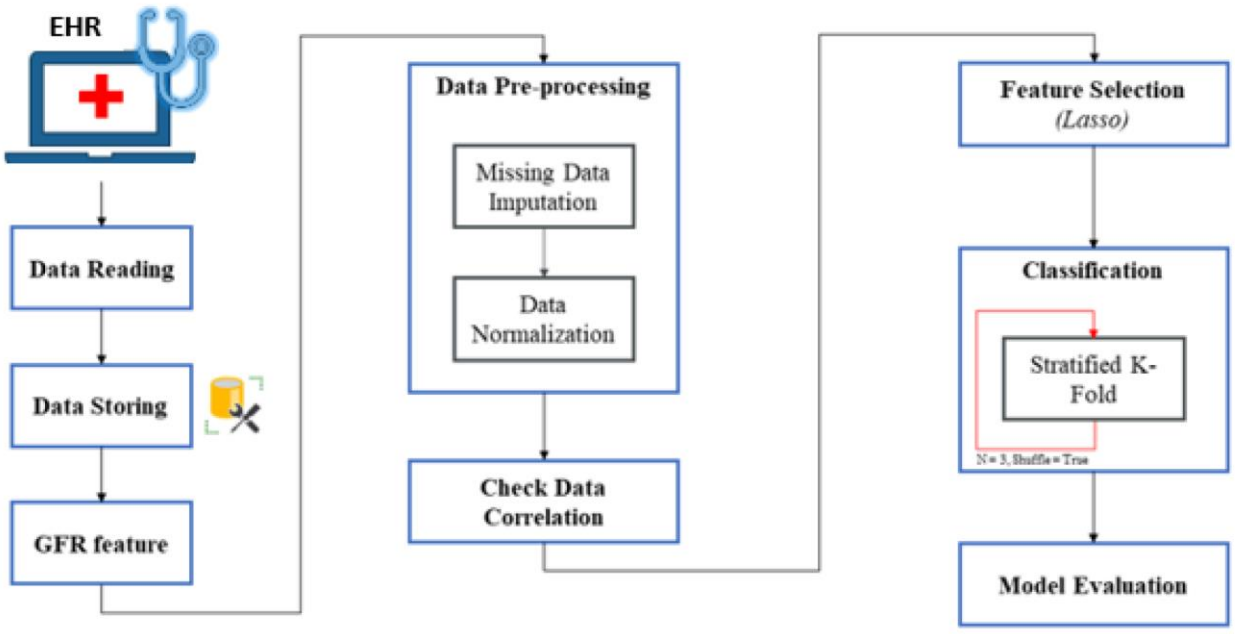

Figure 3.18 Summary of the various steps taken to obtain the model

All the aforementioned information from the CEHRs of the cardiological ward of Villa Scassi hospital was extracted and we stored in MS SQL Server database. Clinicians record in the CEHRS the demographic and anamnestic data and daily the administered therapies at the time of patient's hospitalization. Then, they manually report the results of the ecographic exams (FE and VS-

diameter) performed during hospitalization in the HDLET, which is an integral form of the CEHRS. Finally, the laboratory exams results were retrieve automatically and were integrated in the CEHRS by an a hoc view on the HIS, according to the method described in [70].

3.2.4 Data preparation

The set of features is made of:

● ***Continuous numerical features***: age and laboratory tests. For all patients in the EHR database 187 different laboratory tests are recorded, however only 29 belong to the test battery that carried out on patient with HF, whereas the others are occasionally carried out according to specific patient conditions and/or comorbidity. Therefore only for this 29 tests the missing data are below 40%.

The Glomerular Filtration Rate (GFR) both with the value of serum creatinine at admission and at discharge was calculated using the Modification of Diet in Renal Disease (MDRD) [71] formula:

GFR = 175 $\times$ $(Serum\ Creatinine)^{-1.154}$ $\times$ $Age^{-0.203}$ $\times$ 0. 742 $(if\ female)$

This feature was added because the renal function is very important for HF management. Several important medications used in HF therapies, including ACE inhibitors, may be associated with an increased risk for adverse events in patients with renal insufficiency.

Current HF guidelines lack recommendations for the management of patients with both conditions, as they are often underrepresented in clinical trials[72].

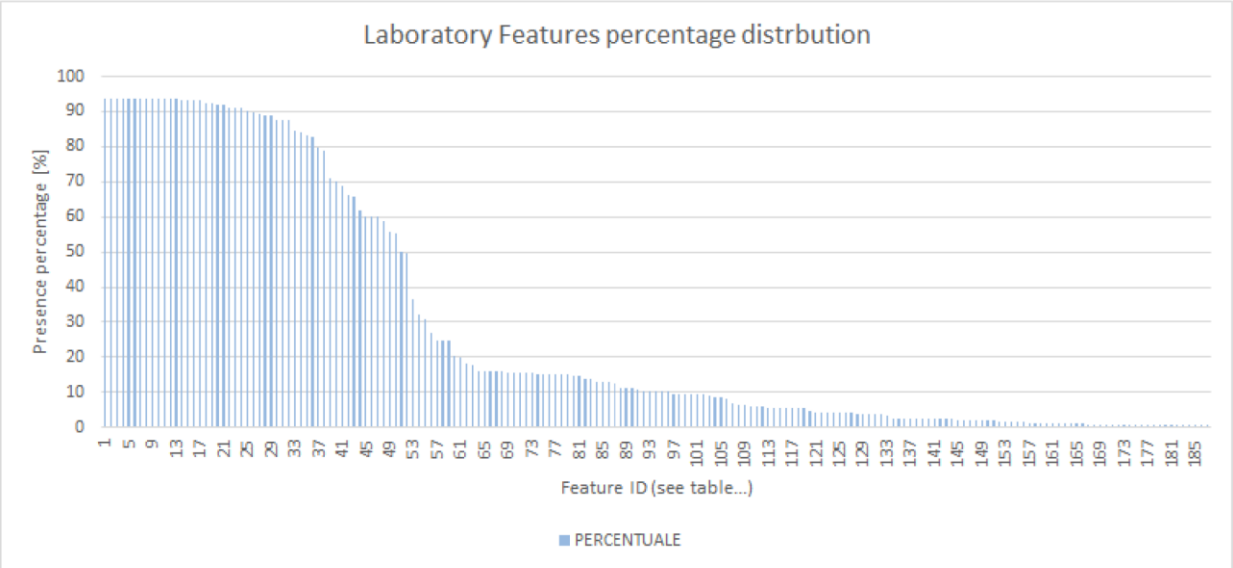

Figure 3.19 Laboratory Feature percentage distribution

● ***Categorical features:*** sex, values 1 and 0 were assigned to female and male patients

Respectively. For smoker/diabetes/hypertension, 1 assigned to patients that matched this condition at the moment of the hospitalization and 0 otherwise. As related to therapies, the following three main classes of drugs were examined: ACE inhibitors, heparin and sartanics, 1was assigned if the patients assumed them at least once during hospitalization (we identified drugs prescriptions through the AIC code) and 0 otherwise. We studied these specific classes as the survival of patients with HF can increase with the use of ACE inhibitors and spironolactone. All major guidelines on heart failure recommend ACE inhibitors as standard therapy for patients with heart failure and left ventricular dysfunction [73].

Once all features to include in the analysis were identified, a correlation analysis was caried out keeping only one among the features correlated with a score higher than 90% (the choice of the features to be removed has been made following the advice of the clinician.

3.2.5 Missing values management

Data preprocessing is an essential step used to clean the data and make it useful for any experiment associated with ML or data mining. The dataset often has some missing values. This problem could be addressed in two ways: listwise deletion (or complete case analysis) by removing all the rows with a missing value from the dataset, or imputation methods by estimating the value of missing data. In order to keep the sample as large as possible, the second option was selected. According to literature, a generally effective algorithm is based on K-Nearest Neighbor (KNN). It imputes each sample's missing values using the mean value from n nearest neighbors found in the dataset [74].

3.2.6 Data normalization

Considering that the numerical values associated with each answer belonged to different scales, the second mandatory step in data pre-processing is normalization. In particular the chosen algorithm for data normalization is based on the Z-score:

$$Z = \frac{x - \mu}{\sigma}$$

where μ is the mean and σ is the standard deviation. The Z-score gives an idea of how far from the mean a data point is. It's a perfect strategy to deal with outliers because it measures how many standard deviations are below or above the population mean and raw score [75].

3.2.7 Experimental design

LASSO was used to perform features selection in order to identify and remove the irrelevant, undesired and redundant input features or characteristics that do not affect the accuracy of the ML model. We determined the best regularization term (alpha) was determined among (0,0001; 0,001; 0,01; 0,1; 1) using LassoCV function of sklearn [76] , a K-Fold cross-validation (with K = 5). In particular, the first K-1 folds are used for learning and the remaining fold is held for validation, this is repeated for all the K-folds, so a total of K-folds are fit and evaluated [77]. The hyperparameter selection was performed with LassoCV and the classification with LASSO in a Stratified K-fold cross-validation (with K = 10) and we repeated this process three times, shuffling the data each time, fixing the random states to 1,2,3 to guarantee reproducibility. As each fold of cross-validation in each shuffle identified a specific set of best features the best set among them was selected in a majority voting process. Specifically, how many times (N) a feature had a not null coefficient in the LASSO coefficients' matrix was counted and the N that induced the best classification performance in terms of accuracy, precision, recall and f1-score was determined.

Specifically, the SVM classifier was adopted to evaluate the performance. A Gaussian kernel function was used to train the SVM model and GridSearchCV was used to identify the best hyperparameters: regularization parameter C and kernel coefficient gamma. Similarly, to the features selection process, a ten-fold stratified cross-validation was adopted and was repeated three times shuffling the data each time with a fixed set of random states (1,2,3), thus to assess model stability.

The SVM model was trained using all features voted N or more times and was performed this process for all the values of N. It ranged from 0 (no features selection is performed and so all the features were considered) to 10 (number of folds) 3 (number of shuffles) = 30 (features × selected at each fold of each shuffle).

3.2.8 Feature selection

To find the best set of features the metrics trend was analyzed as N varies, recalling that N is the number of times each feature has a not null value in the LASSO coefficients' matrix. For each value of N the SVM model was trained with all the features voted at least N times and then we calculated the mean of each metric value across the ten folds and across the three shuffles was calculated. N = 26 is the best choice in terms of accuracy, precision, recall and f1-score, as it is the value where all the four metrics trends reach a peak (Figure 3.20).

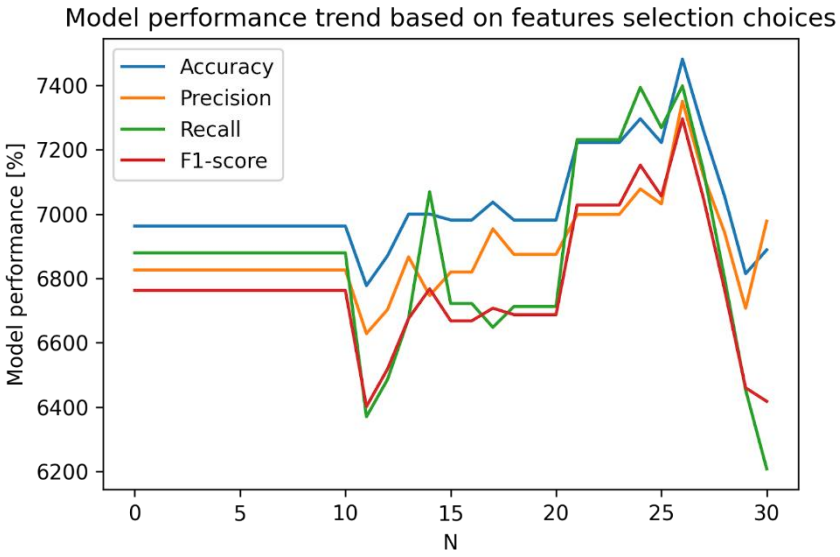

Figure 3.20 The mean of each metric value across the ten folds and across the three shuffles

The best set of features is composed of 26 features and Figure 3.21 shows the mean importance obtained in the voting process by each of them.

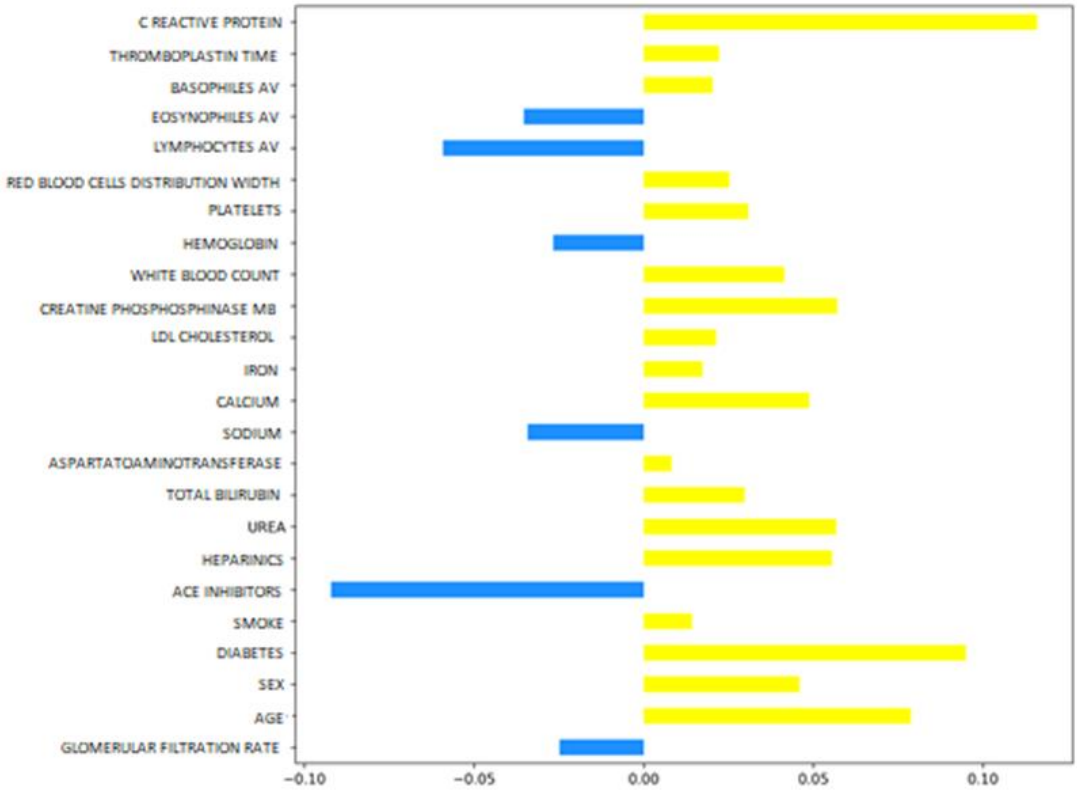

Figure 3.21 Features importance at best N

The absolute value of each feature indicates its importance in order to predict the outcome. The features with a positive weight support the prediction of the outcome when it assumes value equal to 1 (HF patients deceased), otherwise the features with a negative weight support the prediction of the outcome when it assumes value equal to 0 (HF patients not deceased).

3.2.9. Classification performance with the best set of features

Figure 3.22 shows the classifier performance in terms of accuracy, precision, recall and f1-score across the shuffles (blue, orange and green) with the selected best set of features. For each shuffle all 10 values of accuracy, precision, recall and f1-score (one for each fold) are displayed and the first, second and third quartiles are highlighted. The median values of all the aforementioned metrics are stable across shuffles and they range between 75% and 79%. The overall performance of the SVM classifier is always above 60% considering all the metrics. This demonstrates the stability of the model.

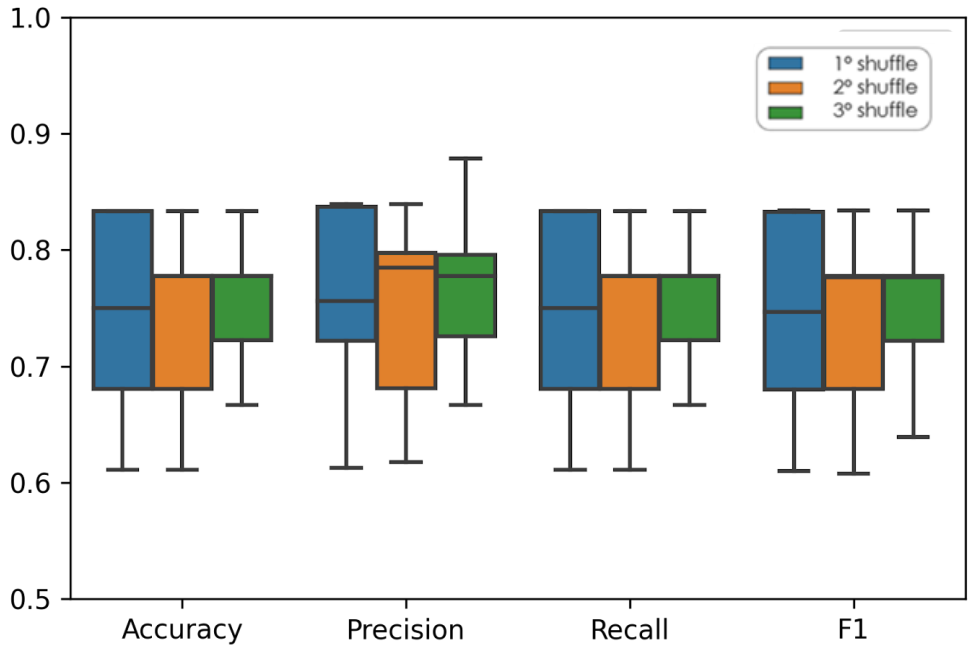

Figure 3.22 The classifier performance in terms of accuracy, precision, recall and f1-score across the shuffles (blue, orange and green) with the selected best set of features

3.2.10 Discussion

The results from this research show that the most influential characteristics (N> = 26) that induce the best performance of the classifier are: GFR, Age, Gender, Diabetes, Smoker, ACEI, Heparinics, Low-density lipoprotein (LDL) Cholesterol, Hemoglobine (Hb), Calcium, Sodium, Iron, Urea, Basophils, Thromboplastin, C-reactive protein (CRP), Lymphocyte. The results confirm the previous studies on the most predictive parameters for heart failure. Various studies reported that

plasma CRP has higher levels in patients with HF [78] and that there is a direct relationship between elevated plasma CRP and the progression of HF [79].

Bilirubin and AST are an indicator of the health of the liver and in literature there are several studies that have attempted to explain the cardiovascular-hepatic relationship documented with abnormal liver function test results in patients with HF [80].

Several studies suggest that a lower hemoglobin level is associated with an increased risk of death in patients with HF [81], [82] whereas others do not [83][84]. Whether anemia predicts adverse outcomes independent of other prognostic factors, such as kidney dysfunction or other confounders, is not entirely clear.

Several observational studies have shown that iron deficiency is associated with a rise in mortality in patients with HF. The latest HF Guidelines recommend routine evaluation of iron deficiency in patients with HF and ferric carboxymaltose therapy for alleviating symptoms determined by cardiac failure, enhancing quality of life and effort capacity [85].

Depending on the connections with the hospital database, the optimal would be to be able to connect with the file that has the data organized in CDA because using the file we could access all the examinations carried out by the patient in the period of interest and not only those which were carried out in the hospital where the patient was hospitalized. This would allow to work on a larger dataset with more features which would be a very useful of extension of this research.

However, in order to be truly effective, this connection must also include an interaction with terminological services to allow an adequate level of semantic standardization allowing a correct automatic interpretation of the parameters measured by different entities [86].

3.3 Predicting the outcome of heart failure against chronic-ischemic heart disease in elderly population

ML models for cardiovascular diagnostics have been used to discriminate among diseased and non-diseased subjects [87]–[89] , to predict cardiovascular risk [90] [91] , to estimate expected LDL level [92] , to predict Cardiac Amyloidosis (CA)[93]. Models operate on fixed parameters of interest, such as: biochemical variables (most common scenario) [90][87][91], status variables[88][89], [91],

demographic variables [91]. Parameters, such as: Sex, Blood Pressure, Heart Rate, Diabetes, Hyper cholesterol, Body Mass Index (obesity), High-density lipoprotein (HDL) , LDL, total cholesterol and triglycerides have been used as covariates in ML models. Some studies have even compared the performance of different ML models: [87], [89] for cardiovascular discrimination. Models' performance has been evaluated according: confusion matrix, precision, recall, f1-score, accuracy [56], Area under the ROC Curve (AUC) score under the receiver operating characteristic (ROC) or Precision-Recall (PR) curves [91], [93] [94] [95].

3.3.1 Study aims

This research aims to decrease the number of misdiagnosed cases of heart failure against chronic-ischemic heart disease according to the prediction of specific blood analysis parameters applying ML. Nine biochemical variables of interest: Hb, Serum Creatinine, LDL, HDL, Triglycerides, Alanine Aminoransferase (ALT), Aspartate Aminoransferase (AST), High-sensitive Cardiac Troponin I(hs-cTnI) and CRP were analyzed in 167 patients diagnosed with chronic-ischemic heart disease and heart failure in order to identify specific combination of biochemical variables (predictors) that provides on average excellent ability to discriminate and predict the outcome of heart failure against chronic-ischemic heart disease. Logistic regression was used as a core ML model and Receiver Operating Characteristic (ROC) and Precision-Recall (PR) curves were used as means to evaluate models' predictive capacity. The individual predictive potential of each parameter was also investigated and findings are reported based on comprehensive computational analysis in Python 3.9.

3.3.2 Main findings

- Hb and HDL unit-increase reduces the odds of HF against CIHD for 21.18% and 3.83% on average, p-value<0.05;

- AST, ALT and CRP unit-increase increases the odds of HF against CIHD for 3.43%, 2.46% and 4.11% on average, p-value<0.05;

- Logistic regression-based model upon covariates: Hb + Serum Creatinine + AST + hs-cTnI + CRP provides on average excellent discrimination between heart failure and chronic-ischemic heart disease, The Area under the receiver operating characteristic (AUROC) =0.805 (20-fold cross-validation mean AUROC score reported);

3.3.3 Data and materials of analysis

The results from a full blood panel tests of 167 cardiac patients, diagnosed with CIHD – 108 and HF)– 59, onset to hospitalization at cardiology ward in the Villa Scassi hospital in the period February 2020 – March 2021 were considered. ARCHITECT c16000 clinical chemistry analyser (ABBOTT) and ADVIA 2120/2120i (SIEMENS) hematology analyzer were used to access 9 biochemical variables of interest $\sum$ = {LDL (mg/dL),HDL (mg/ dL), Triglycerides (mg/dL),Serum Creatinine (mg/dL), ALT (U/L), AST (U/L), hs − cTnI (pg/mL), Hb (g/dL), CRP (mg/L)}. Blood test files were extracted by SIO SIVIS Health Information System. Study participants mean age ± standard deviation was 69.74 ± 12.05 years. CIHD patients had mean age of 68.85 years, SD=11.3, while HF patients had mean age of 71.373 years (SD=13.27). About three quarters or 74.85% of study participants were male and 25.15% female. Totally 77.78% of CIHD patients were male and 22.22% female. In the HF group there were 69.49% male patients and 30.51% female patients. For CIHD and HF groups, for all parameters in Σ, we computed: minimum (min), first quartile (Q1), median (Q2), third quartile (Q3), maximum (max), mean, standard deviation (SD), range, interquartile range (IQR) and skewness (sk) were computed, Table 1. range, interquartile range and standard deviation as measures of variability were used, Table 1. Skewness $s_k = \frac{\sum_{i=1}^{N}(x_i - mean)^3}{(N-1)SD^3}$ was computed to measure distribution's deviation relative to perfect symmetry and get the direction of outliers. As per rule of thumb: $-0.5 < sk < 0.5$ for approximately symmetrical distribution, $0.5 \leq sk < 1 (-1 < sk \leq -0.5)$ for moderate positive(negative) skewness and $sk \geq 1 (sk \leq -1)$ for positive(negative) skewness. The distribution of each parameter in both control groups was plotted: CIHD (Fig. 3.23), HF (Fig. 3.24).

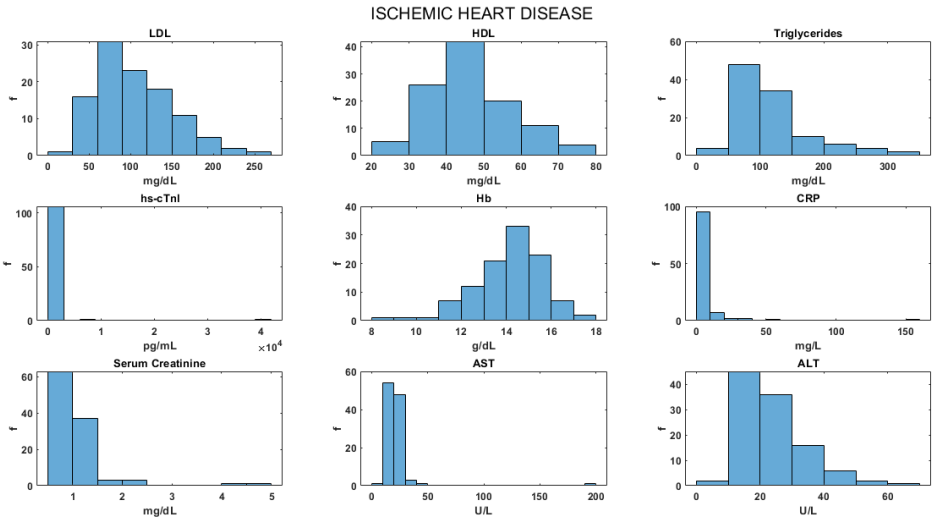

Figure 3.23. Biochemical variables histogram – IHD group

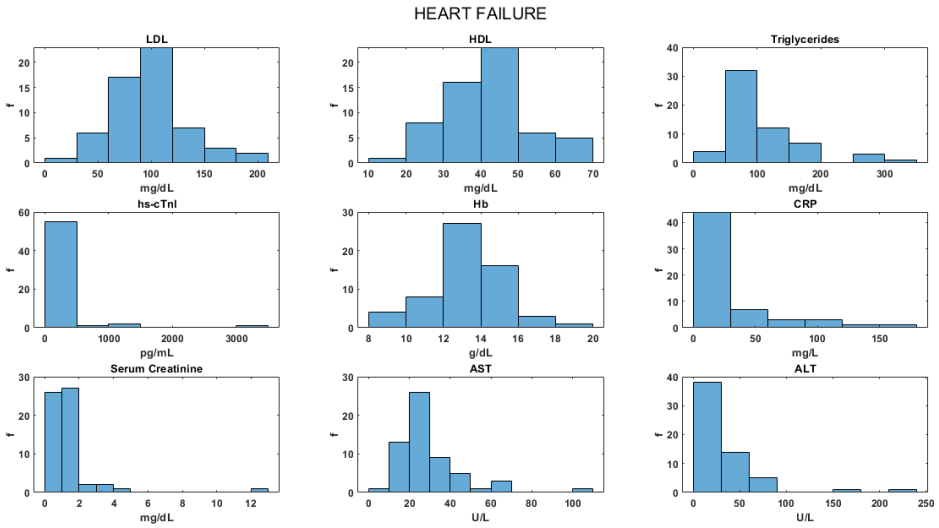

Figure 3.24. Biochemical variables histogram – HF group

No major difference in HDL, Triglycerides and Hb variability was found among IHD and HF group, Table 1, Fig.3.25. LDL had higher variability in IHD compared to HF group: $\mathrm{IHD}_{\mathrm{LDL,SD}} = 46.7\ \mathrm{mg/dL}$; $\mathrm{IHD}_{\mathrm{LDL,IQR}} = 68.25\ \mathrm{mg/dL}$; $\mathrm{IHD}_{\mathrm{LDL,range}} = 218\ \mathrm{mg/dL}$; ($\mathrm{HF}_{\mathrm{LDL,SD}} = 36.09\ \mathrm{mg/dL}$; $\mathrm{HF}_{\mathrm{LDL,IQR}} = 29\ \mathrm{mg/dL}$; $\mathrm{IHD}_{\mathrm{LDL,range}} = 186\ \mathrm{mg/dL}$), Table 1, Fig. 3.25. LDL mean and LDL median scored approximately the same in both groups, Table 1. On the other hand, high-sensitive cardiac Troponine I (hs-cTnI) was unevenly distributed, Table 1. HF group had higher hs-cTnI median (21.9 pg/mL) and IQR (63.7 pg/mL) that is approximately six times IHD IQR of 11.65 pg/mL, Table 1. At the same time, hs-cTnI mean (470 pg/mL), standard deviation (3916.98 pg/mL) and range (40060.7 pg/mL) were higher in IHD control group, Table 1. CRP ranged about the same in both group (Table 1, Fig. 3.25), but there was significant difference in CRP mean, standard deviation, median and IQR between groups, Table 1, Fig. 3.25. Higher values are attributed to HF: $\mathrm{IHD}_{\mathrm{CRP,mean\pm SD}} = 6.29 \pm 16.59\ \mathrm{mg/L}$ ($\mathrm{HF}_{\mathrm{CRP,mean\pm SD}} = 25.4 \pm 35.59\ \mathrm{mg/L}$); $\mathrm{IHD}_{\mathrm{CRP,median}} = 1.75\ \mathrm{mg/L}$ ($\mathrm{HF}_{\mathrm{CRP,median}} = 11.1\ \mathrm{mg/L}$); $\mathrm{IHD}_{\mathrm{CRP,IQR}} = 4.03\ \mathrm{mg/L}$ ($\mathrm{HF}_{\mathrm{CRP,IQR}} = 26.5\ \mathrm{mg/L}$), Table 1. Serum Creatinine was more variable in HF group, Table 1. Higher ALT variability was also specific to HF control group: $\mathrm{IHD}_{\mathrm{ALT,SD}} = 10.52\ \mathrm{U/L}$; $\mathrm{IHD}_{\mathrm{ALT,IQR}} = 12.5\ \mathrm{U/L}$; $\mathrm{IHD}_{\mathrm{ALT,range}} = 55\ \mathrm{U/L}$; ($\mathrm{HF}_{\mathrm{ALT,SD}} = 34.53\ \mathrm{U/L}$; $\mathrm{HF}_{\mathrm{ALT,IQR}} = 22.5\ \mathrm{U/L}$; $\mathrm{HF}_{\mathrm{ALT,range}} = 214\ \mathrm{U/L}$), Table 1, Fig. 3.25. HF ALT mean was 32.71 U/L, while IHD ALT mean was 23.08 U/L, Table 1. We computed mean IHD AST of 21.43 U/L and 28.49 U/L mean HF AST, Table 1.

Table 1. Biochemical parameters characteristics – IHD and HF control groups

Parameter	min	Q1	Q2	Q3	max	mean	SD	range	IQR	skewness

LDL (mg/dL) IHD	26	66	98.5	134.25	244	105.528	46.703	218	68.25	0.8
LDL (mg/dL) HF	21	79	98	108	207	98.678	36.087	186	29	0.581
HDL (mg/dL) IHD	23	38	43.5	52	80	45.796	11.864	57	14	0.721
HDL (mg/dL) HF	18	32.5	41	45	70	40.847	11.117	52	12.5	0.49
Triglycerides (mg/dL) IHD	41	82.75	101	136.25	334	119.139	60.615	293	53.5	1.408
Triglycerides (mg/dL) HF	41	69	89	124	326	106.966	61.065	285	55	1.942
hs-cTnI (pg/mL) IHD	0.1	3.25	6.35	14.9	40060.8	470.005	3916.982	40060.7	11.65	9.709
hs-cTnI (pg/mL) HF	1	13.25	21.9	76.95	3336.1	160.992	483.238	3335.1	63.7	5.286
Hb(g/dL) IHD	8.1	13.2	14.15	15.1	17.2	14.062	1.56	9.1	1.9	-0.783
Hb(g/dL) HF	8.1	12.15	13.4	14.7	18.5	13.297	2.133	10.4	2.55	-0.058
CRP (mg/L) IHD	0.3	0.9	1.75	4.925	155.8	6.291	16.593	155.5	4.025	7.164
CRP (mg/L) HF	0.3	4	11.1	30.5	150.7	25.4	35.591	150.4	26.5	1.995
Serum Creatinine (mg/dL) IHD	0.58	0.8	0.965	1.09	4.56	1.07	0.554	3.98	0.29	4.184
Serum Creatinine (mg/dL) HF	0.59	0.87	1.05	1.29	12.83	1.408	1.653	12.24	0.42	5.83
AST (U/L) IHD	7	16	19	23	192	21.426	17.463	185	7	8.71
AST (U/L) HF	6	20	23	35	104	28.492	16.285	98	15	2.208
ALT (U/L) IHD	6	15	21	27.25	61	23.083	10.515	55	12.5	1.117
ALT (U/L) HF	6	14.5	23	37	220	32.712	34.526	214	22.5	3.518

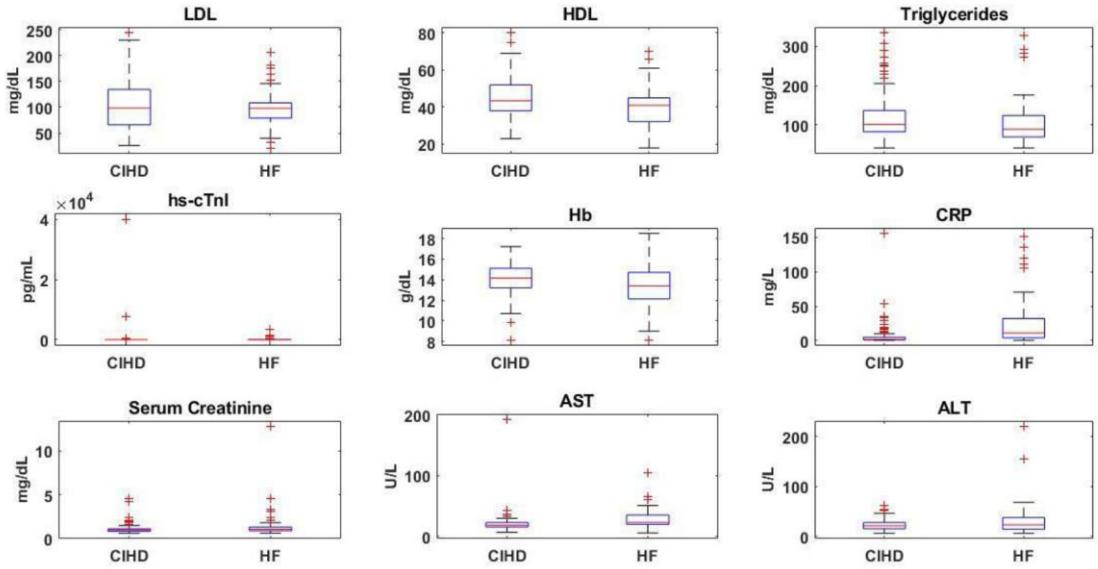

Figure 3.25 CIHD versus HF parameters distribution

3.3.4 Computational analysis methods

The dataset of 167 patients was used which includes data on 9 explanatory variables of interest Σ = {Hb, Serum Creatinine, LDL, HDL, Triglycerides, ALT, AST, hs − cTnI, CRP} to examine the potential use of each parameter included in Σ as predictor to the outcome of HF against CIHD and we aimed to find subset of biochemical variables from Σ that provides best discrimination between HF and CIHD. Logistic regression was used as a core model in our computational analysis. Parameters' predictive potential was examined in Python 3.9 convenience interface statsmodels.formula.api and Scikit-learn (Sklearn) library (Python 3.9) was used to measure mean diagnostic capacity provided under particular model section (combination of predictors) based on 20-fold cross-validation.

To identify statistically significant predictors on HF against CIHD single variable logistic regression analysis was performed in statsmodels.formula.api (Python 3.9). Odds ratios (log odds ratios) of HF against CIHD for significant regressors (pvalue< 0.05) were reported. As method for model estimation Maximum Likelihood Estimation (MLE) was used, [96]. For each model: the maximum of the log likelihood function: $log(L(m))$ and McFadden's log likelihood ratio was reported (McFadden, 1974) R^2: $R^2_{MF} = 1 - \frac{\boldsymbol{log(L(m))}}{\boldsymbol{log(L(m_0))}}$ as a measure for the goodness of fit, based on the improvement of the model m relative to the null model m_0(the model that contains intercept only). Comprehensive computational analysis was carried out, based on: all data fits, fits having excluded extreme outliers and fits having excluded regression influential points only. Points v_i such as: v_i <

$Q1 - 3IQR$ or $vi > Q3 + 3IQR$ are considered as extreme outliers and their impact on regression was examined. On the other hand, deviance residuals $r_i{}^D$[97] were computed to measure the exact level of discrepancy between the current fit and the ideal fit at each point v_i, thus suggesting points vi that significantly affect the course of the logistic curve. Deviance residuals $r_i{}^D$ were computed as:

$r_i^D = s_i\sqrt{-2\{Y_i \log(\pi_i) + (1 - Y_i)\log(1 - \pi_i)\}}$, s_i = +1 if Y_i = 1 (HF) and s_i = −1 if Y_i = 0 (CIHD), such as: Y_i is dichotomous output for data point v_i and π_i is the value of HF probability curve from the estimated model at point v_i . Values v_i for which: $r_i{}^D > 2$ or $r_i{}^D < -2$ were considered as highly influential and their impact on the goodness of fit was analyzed.

Backward stepwise elimination methodology was applied [98]to select combination of significant predictors only, p-value<0.05. Throughout the process we monitored likelihood-ratio test $\lambda_{LR} = -2\log\left(\frac{L(m_r)}{L(m)}\right)$ p-value or the probability that further nested model restriction mr would result in better fit relative to the current fit m. For selected covariates the joint diagnostic capacity of logistic regression as a binary predictor of diagnosis was examined: 0 for chronic-ischemic heart disease and 1 for heart failure. For that purpose, 20-fold repeated stratified cross-validation was applied. Repeated cross-validation provided an unbiased estimate of the mean discrimination capacity of the model, while stratification preserved the same ratio of CIHD to HF patients in the train and test splits due to the presence of moderate class imbalance in our dataset (108 CIHD patients (64.7%), 59 HF patients (35.3%)). The set of 167 cardiac patients was shuffled each time the cross validation was repeated that ensured training and testing logistic regression models for different combinations of cardiac patients. The overall diagnostic performance was summarized by mean AUROC score (area under the receiver operating characteristic). To estimate the average precision of the model on HF predictions (the positive or the minority class) x the area under the mean PR curve, area under PR curve (AUPRC) was applied.

Significance level was set to 0.05. Logistic regression was fitted five times, such as the most insignificant predictor (highest p-value) was discarded from the domain Σ, until there were left only significant predictors (p-value<0.05), Table 2. As we refitted the regression, λLR p-value gradually improved, Table 2. We gradually discarded: ALT (U/L) (p-value=0.764), LDL (mg/dL) (p-value=0.628), Triglycerides (mg/dL) (p-value= 0.410) and HDL (mg/dL) (p-value=0.192) from Σ (Table 1), until all left covariates were statistically significant: Hb+SerumCreatinine+AST+hs-cTnI+CRP, Table 2.

Table 2. Selection of significant predictors (backward stepwise elimination methodology)

Model	$\boldsymbol{\lambda_{LR}}$ p-value	Hb (g/dL)	Serum Creatinine (mg/dL)	AST (U/L)	ALT (U/L)	LDL (mg/dL)	HDL (mg/dL)	Triglycerides (mg/dL)	hs-cTnI (pg/mL)	CRP (mg/L)

1	2.495×10^{-9}	0.012	0.088	0.001	~~0.764~~	0.622	0.122	0.357	0.005	0.008
2	9.095×10^{-10}	0.010	0.089	0.000		~~0.628~~	0.124	0.358	0.007	0.008
3	3.320×10^{-10}	0.011	0.092	0.000			0.142	~~0.410~~	0.007	0.008
4	1.390×10^{-10}	0.008	0.079	0.000			~~0.192~~		0.006	0.006
5	**8.944×10^{-11}**	**0.010**	**0.049**	**0.000**					**0.004**	**0.006**
Best model		**Hb**	**Serum Creatinine**	**AST**	~~ALT (U/L)~~	~~LDL (mg/dL)~~	~~HDL (mg/dL)~~	~~Triglycerides (mg/dL)~~	**hs-cTnI**	**CRP**

We applied 20-fold repeated stratified cross-validation to the input dataset of 167 cardiac patients to check the joint diagnostic capacity of suggested selection: Hb+SerumCreatinine+AST+hs-cTnI+CRP. Prior cross-validation, we applied data standardization. Applying equation: $\boldsymbol{z_i = \frac{x_i - \mu}{\sigma}}$ (μ predictor mean value, σ predictor standard deviation), predictors' values x_i were transformed to z_i – distribution with mean value 0 and standard deviation 1. We used 4:1 train-test ratio split or 80% of the cardiac patients (134 cardiac patients) were used to fit logistic regression models and the remaining 20% (33 cardiac patients) were used to test the models. This was repeated 4 times on shuffles to the input dataset, that provided training/testing models for different combinations of cardiac patients. Train-test ratio of 4:1 means that we spilt the dataset into 5 folds, such as: 4-folds were used to train the model and 1-fold was used to test the model, Fig. 3.26. Since there are 5 different folds that can be used for testing and the remining 4 for training, each repetition resulted in 5 trained and tested models, Fig. 3.26. Given that we repeated the cross validation 4 times, we were able to estimate the diagnostic capacity of totally 20 models of logistic regression.

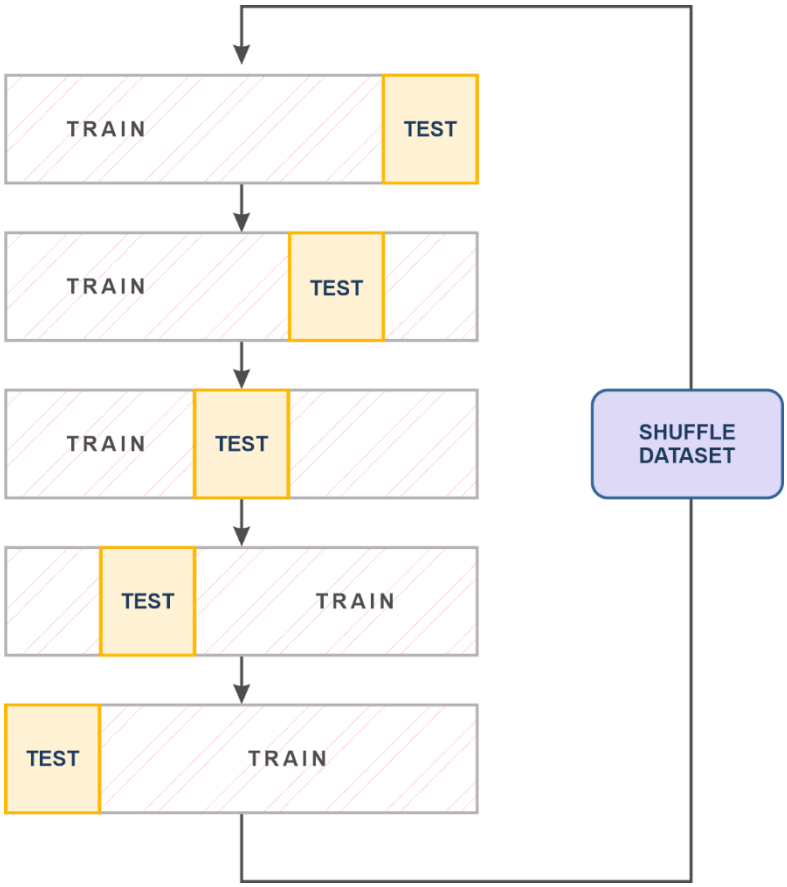

Figure 3.26 Cross-validation – 4:1 train-test ratio split, repeated 4 times

For trained models test splits were used to compute ROC [99] and PR curves [100]. ROC and PR curves are powerful means to estimate diagnostic ability of the model over a range of classification thresholds (THR), $0 \leq THR \leq 1$. This means that instead of examining the discrimination capacity of the model at fixed cut-off point – classification threshold (*by default THR = 0.5), it is examined for all real numbers in the range [0-1] taken as decision thresholds. For illustration, given a trained model under: Hb + Serum Creatinine + AST + hs-cTnI + CRP, for each patient in the test set $p(HF)$ (Equation 1) is computed for standardized: Hb, Serum Creatinine, AST, hs-cTnI, CRP values. IF $p(HF) > THR$ the patient is classified as HF patient, otherwise as CIHD patient and this is done not just for one cut-off THR, but for all decision thresholds THRs in the range [0-1].

$$p(HF) = \frac{e^{\alpha+\beta_1 Hb+\beta_2 Serum\ Creatinine+\beta_3\ AST+\ \beta_4 hs-cTnI+\beta_5 CRP}}{1+e^{\alpha+\beta_1 Hb+\beta_2 Serum\ Creatinine+\beta_3\ AST+\ \beta_4 hs-cTnI+\beta_5 CRP}},\ 0 \leq THR \leq 1 \quad \textbf{\textit{Eq. (1)}}$$

$p(HF)$: probability of HF

ROC curve summarizes discrimination potential of the model to assign patients to the right class. It is plotted as trade-offs between true positive rate (TPR) (also referred as Recall or Sensitivity)

(Equation 2) and false positive rate (FPR) (Equation 3) at all possible classification thresholds THR, $0 \leq THR \leq 1$. In our case, TPR or the Recall measures how many of the real HF patients were ranked as HF, while FPR measures the fraction of CIHD patients that were mispredicted as HF patients. Since there is a relation between FPR and TNR(or Specificity) or how many of CIHD patients were actually predicted as CIHD, such as: FPR=1-TNR, ROC curve may be also seen as plot of Sensitivity versus 1-Specificitiy at different decision thresholds. The area under the ROC curve AUROC may be seen as probability that randomly selected HF patient is ranked as more likely to be HF patient than randomly selected CIHD patient.

$$\boldsymbol{TPR\ (Recall) = \frac{TP}{TP+FN}}\ \textbf{Eq. (2)}$$

TP (true positives): number of HF patients predicted as HF patients

FN (false negatives): number of HF patients mispredicted as CIHD patients

$$\boldsymbol{FPR = \frac{FP}{FP+TN}}\ \textbf{Eq. (3)}$$

FP (false positives): number of CIHD patients mispredicted as HF patients

TN (true negatives): number of CIHD patients predicted as CIHD patients

Given that in model's performance for true negatives (CIHD patients predicted as CIHD) is not interesting, PR curve offers selective estimation of model's diagnostic ability, biased towards the positive class – HF. PR curve is plotted as trade-offs between Precision (Equation 4) – how many of the predicted HF patients were actually true HF patients and Recall (Equation 2) – how many of the true HF patients were actually predicted as HF patients at every single classification threshold THR, $0 \leq THR \leq 1$. The area under the PR curve AUPRC is the average precision on HF predictions.

$$\boldsymbol{Precision = \frac{TP}{TP+FP}}\ \textbf{Eq. (4)}$$

In the cross-validation, totally 20 models of logistic regression were trained and tested and the same number of ROC and PR curves were computed. Trapezoidal rule was used to compute AUROC [101] [102] (Equation 5) and AUPRC [103] (Equation 6).

$$\boldsymbol{AUROC = \sum_{i=1}^{N} TPR(i) \times \Delta FPR(i)}\ \textbf{Eq. (5)}$$

$$\boldsymbol{AUPRC = \sum_{i=1}^{N} Precision(i) \times \Delta Recall(i)}\ \textbf{Eq. (6)}$$

Δ: sampling interval

$TPR(i), Precision(i)$: $i'th$ TPR, Precision sample

3.3.5 Implementation of the Logistic regression model

Single-variable logistic regression analysis in Python 3.9 statsmodels was performed. For all models the reported results were: McFadden's Pseudo R^2, the maximum of the log likelihood function $log(L(m))$, predictor's regression coefficient: log odds ratio (odds ratio), 95% confidence interval and the p-value. For each model the probability of HF against CIHD curve – p(HF) was computed and plotted in addition to extreme outliers and residual deviances r_i^D, Fig. 3.27. Both McFadden's Pseudo R^2 and r_i^D may be taken as measures for the goodness of fit, expect that r_i^D s are suitable for visual inspection of the goodness of fit, Fig. 3.27. The more r_i^D s asymptotically approach the p(HF) curve, the more the goodness of fit is improved, Fig. 3.27.

Plots matched numerical results, Table 3-5, Fig. 3.27. For parameters that are significant predictors of the outcome: 0(CIHD)/1(HF), sigmoidal (S-shaped) p(HF) curves were plotted, either positive or negative, Fig. 3.27, Table 3. For insignificant predictors p(HF) the logistic S-shape lacked and it was linear most of the time, Fig. 3.27. Of all insignificant predictors, only hs-cTnI becomes significant as predictor, if extreme outliers are removed, Table 4, Fig. 3.28. In principle, removing extreme outliers for significant predictors did not improved the goodness of fit (estimated by McFadden's Pseudo R^2 and r_i^D distribution), Fig. 3.28. The goodness of fit for significant predictors was improved by discarding highly influential residuals only: $r_i^D > 2$ ($r_i^D < -2$), Table 5, Fig. 3.29

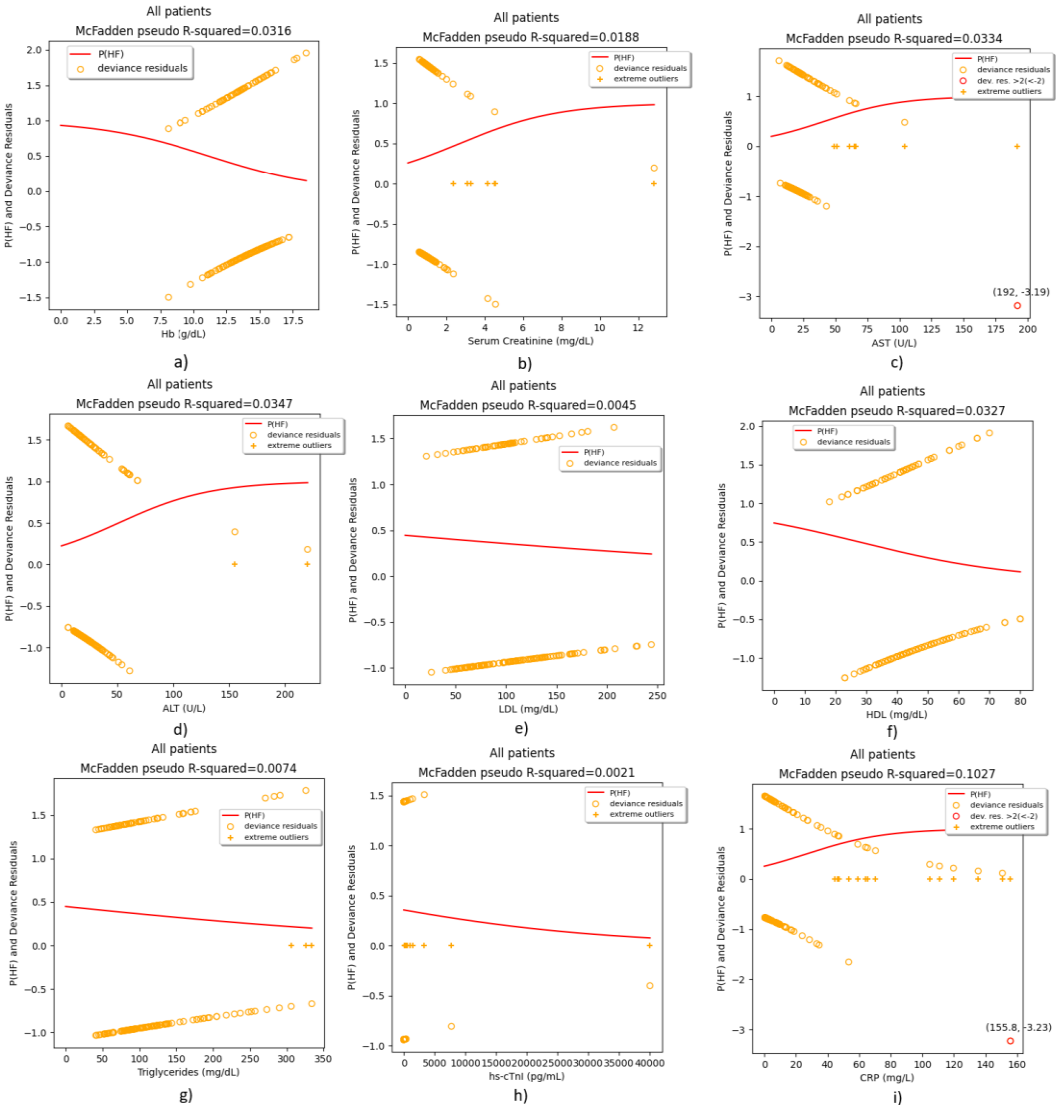

Figure 3.27 Regression fits – all patients included

Regressors: Hb, AST, ALT, HDL and CRP were found as independent, statistically significant predictors (p-value<0.05) of HF against CIHD, Table 3. Hb and HDL negative P(HF) curve (Fig. 3.27) indicates on reduced odds of HF against CIHD having increased Hb or HDL, while AST, ALT and CRP positive P(HF) curve indicates on increased odds of HF against CIHD having increased

AST, ALT or CRP (Fig. 3.27). We have found that (Table3):

I. g/dL increase of Hb reduces the odds of HF against CIHD for 21.18% on average, 95% CI=[5.34 – 34.37]%, p-value=0.011;
II. II. U/L increase of AST increases the odds of HF against CIHD for 3.43% on average, 95% CI=[0.33 – 6.63]%, p-value=0.03;
III. III. U/L increase of ALT increases the odds of HF against CIHD for 2.46% on average, 95% CI=[0,33 – 4,64]%, p-value=0.024;
IV. IV. mg/dL increase of HDL reduces the odds of HF against CIHD for 3,83% on average, 95% CI=[0,88 – 6,69]%, p-value=0.011;
V. V. mg/L increase of CRP increases the odds of HF against CIHD for 4.11% on average, 95% CI=[1,71 – 6,58]%, p-value=0.01.

Table 3. Odds ratio (log odds ratio) of HF against CIHD for significant predictors

	McFadden's Pseudo R^2	$log(L(m))$	Log odds ratio	Log odds ratio 95% CI		Odds ratio	Odds ratio 95% CI		p-value
Hb (g/dL)	0.03157	-105.04	-0.2380	-0.421	-0.055	0,788229	0,656331	0,946635	0.011
AST (U/L)	0.03337	-104.84	0.0337	0.003	0.064	1,034306	1,003271	1,066301	0.030
ALT (U/L)	0.03472	-104.69	0.0243	0.003	0.045	1,024626	1,003264	1,046443	0.024
HDL (mg/dL)	0.03271	-104.91	-0.0391	-0.069	-0.009	0,961701	0,933122	0,991154	0.011
CRP (mg/L)	0.1027	-97.319	0.0403	0.017	0.064	1,041128	1,017065	1,065761	0.001

Serum Creatinine (p-value=0.115), LDL (p-value=0.328), Triglycerides (pvalue=0.219) and hs-cTnI (p-value=0.593) were insignificant in predicting the outcome of HF against CIHD. For Triglycerides and LDL as regressors, P(HF) curve was linear, while U-shaped curve for hs-cTnI was plotted, instead of the regular S-shaped curve, Fig. 3.27. No $r_i^D > 2$ ($r_i^D < -2$) points were found for insignificant predictors, but only significant number of extreme outliers in Serum Creatinine (8) and hs-cTnI (20), Fig. 3.27.

Insignificant regressors' extreme outliers were removed and models were refitted again, Fig. 3.28. In that case hs-cTnI becomes significant as independent predictor of HF against CIHD, increasing the odds of HF against CIHD for 2.68% on average, 95% CI=[0.98 – 4.41]%, p-value=0.002 for each

pg/mL increase, Table 4. This time instead of Ushaped curve, regular S-shaped p(HF) curve was computed, Fig. 3.28. Removing extreme outliers in Serum Creatinine (8) did not remove p(HF) linearity and no regular S-shaped curve was computed for excluding extreme outliers in Triglycerides (3), Fig. 3.28. Serum Creatinine (p-value=0.211) and Triglycerides (p-value=0.175) were again insignificant as predictors. When it comes to significant predictors, Hb and HDL did not include extreme outliers, while for AST(7), ALT(2) and CRP(14) we recorded slightly improvement of the goodness of fit only for AST (McFadden's Pseudo R 2 increased from 0.0334 to 0.0679), Fig. 3.28.

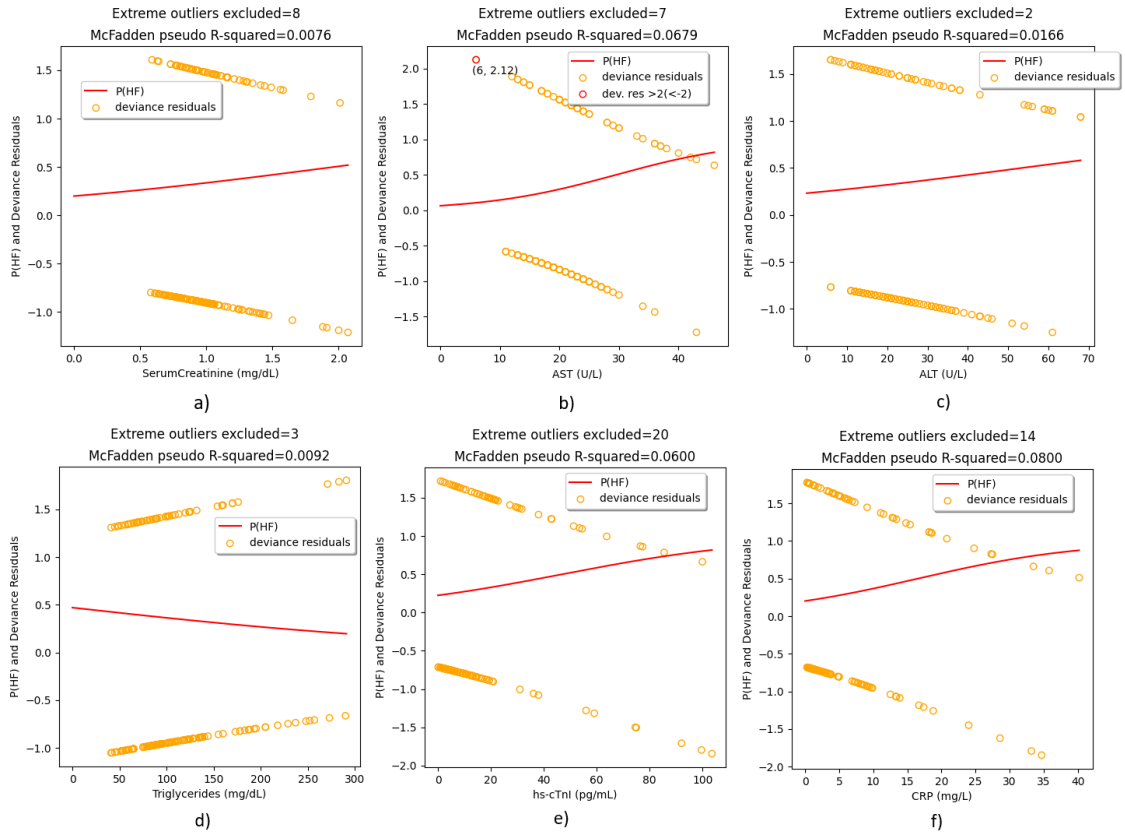

Figure 3.28 Regression fits – extreme outliers discarded

Table 4. Odds ratio (log odds ratio) of HF against IHD for hs-cTnI as predictor, extreme outliers excluded

	McFadden's Pseudo R^2	$log(L(m))$	Log odds ratio	Log odds ratio 95% CI		Odds ratio	Odds ratio 95% CI		p-value
hs-cTnI (pg/mL)	**0.05997**	**-86.596**	**0.0265**	**0.010**	**0.043**	**1,026806**	**1,009811**	**1,044086**	**0.002**

Regression highly influential points $r_i{}^D > 2$ ($r_i{}^D < -2$) were found in AST, values: 192 U/L, 6 U/L and CRP, values: 155.8 mg/L, 53.4 mg/L, 34.7 mg/L and 33.2 mg/L, Fig. 3.27. Discarding these points only and refitting logistic regressions again: p(HF) curve Sshape improved, McFadden's

Pseudo R^2 increased from 0.0334 to 0.1339 for AST and for CRP it was doubled, 0.2232 compared to 0.1027 in the initial fit, Fig. 3.29. In Table 5 we report odds ratio (log odds ratio) of HF against CIHD, having removed residuals $r_i{}^D > 2$ ($r_i{}^D < -2$) in AST and CRP. Table 5. Odds ratio (log odds ratio) of HF against CIHD for AST and CRP as regressor, $r_i{}^D > 2$ ($r_i{}^D < -2$) residuals excluded

	McFadden's Pseudo R^2	$log(L(m))$	Log odds ratio	Log odds ratio 95% CI		Odds ratio	Odds ratio 95% CI		p-value
AST (U/L)	**0.1339**	**-92.658**	**0.1074**	**0.057**	**0.157**	**1,113376**	**1,059110**	**1,170422**	**0.000**
CRP (mg/L)	**0.2232**	**-82.874**	**0.1169**	**0.063**	**0.170**	**1,123956**	**1,065557**	**1,185557**	**0.000**

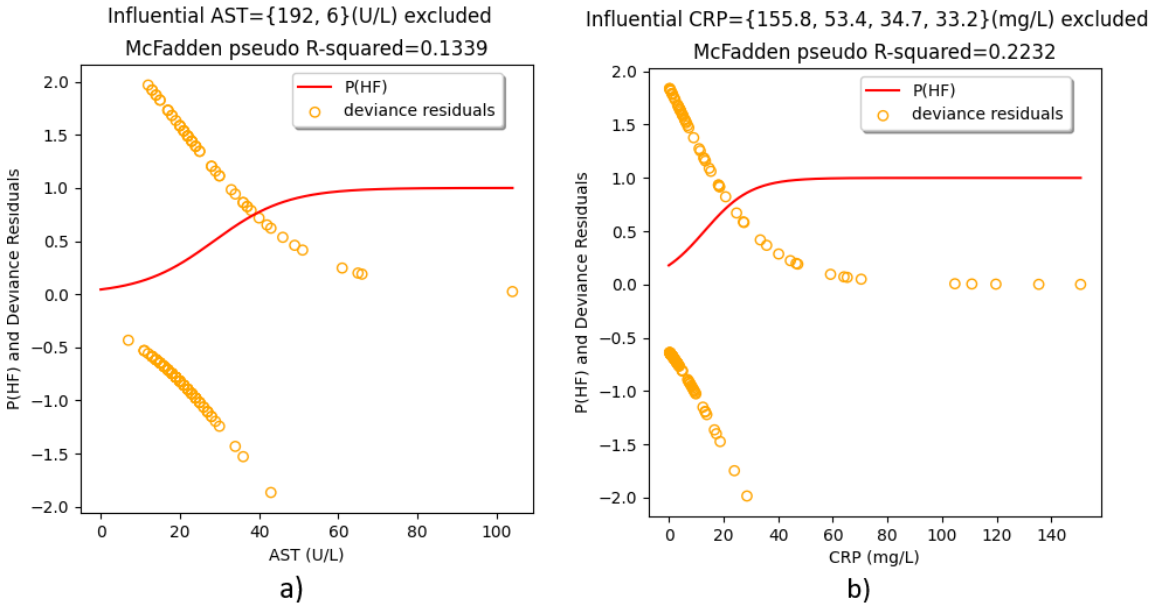

Figure 3.29 Regression fits – $ri\ D > 2$ ($ri\ D < -2$) discarded

Having discarded AST and CRP regression influential residuals $r_i{}^D > 2$ ($r_i{}^D < -2$), it has been found that: VI. U/L increase of AST increases the odds of HF against CIHD for 11.34% on average, 95% CI=[5.91 – 17.04]%, p-value=0.000; VII. mg/L increase of CRP increases the odds of HF against CIHD for 12.4% on average, 95% CI=[6.56 – 18.56]%, p-value=0.000. The mean diagnostic capacity of the combination of statistically significant predictors: Hb + Serum Creatinine + AST + hs-cTnI + CRP (Table 2) in Scikit-learn (Python 3.9) was examined. To detect the impact on discrimination ability having discarded specific covariate, the mean diagnostic ability of all models considered in backwards elimination methodology (Table 2) was analyzed. The impact on discrimination capacity having discarded the least significant of all significant predictors – Serum Creatinine, p-value=0.049 (Table 2) was also examined. Totally 20 different combinations of 134 CIHD+HF patients (80% of data) for models' training and 33 CIHD+HF patients (20% of data) for models' testing were derived from the input dataset of 167 cardiac patients: 108 CIHD + 59 HF patients. Stratification preserved

the same percentage of CIHD (64.7%) to HF (35.3%) patients in training and testing sets, 87 CIHD+47 HF=134 cardiac patients in training sets and 21 CIHD+12 HF=33 cardiac patients in testing sets. For all models, 20 models of logistic regression were computed and models' ROC curves and PR curves were plotted, Fig. (3.30-3.35). From ROC and PR curves the mean ROC and the mean PR curve were computed and the area underneath, Fig. (3.30-3.35), Table 6. The obtained results are relevant and comparable in terms of the impact of covariates upon overall diagnostic ability, because the same combinations of train-test splits for all models' selection were used, Fig. (3.30-3.35), Table 6.

The combination of predictors: **Hb + Serum Creatinine + AST + hs-cTnI + CRP** predicted the true diagnosis: heart failure (1) against chronic-ischemic heart disease (0), 80.5% of the time (mean AUROC=0.805), while the average precision on HF predictions was 71.2% (mean AUPRC=0.712), Table 6, Fig. 3.30.

Other combinations of predictors were generally less accurate than: Hb + Serum Creatinine + AST + hs-cTnI + CRP, Table 6. Mean AUROC=0.769 (mean AUPRC=0.691) was computed for having all covariates included in the model, Table 6, Fig. 3.31. Excluding ALT (p-value=0.764, Table 2) as covariate, mean AUROC=0.776 (mean AUPRC=0.698) was obtained, Table 6, Fig. 3.32. Discarding ALT + LDL (pvalue=0.628, Table 2) as covariates, the mean AUROC was 0.78 (mean AUPRC= 0.702), Table 6, Fig. 3.33. Having discarded ALT + LDL + Triglycerides (p-value=0.410, Table 2) as covariates, mean AUROC=0.792 (mean AUPRC=0.717) was computed, Table 6, Fig. 3.34.

The combination of all significant predictors: Hb + Serum Creatinine + AST + hs-cTnI + CRP (HDL excluded, p-value=0.192, Table 2) provided best discrimination score of 0.805 mean AUROC, Table 6, Fig. 3.30. Further model restrictions did not improve discrimination ability. Having discarded the least significant of all significant predictors – Serum Creatinine (p-value=0.049, Table 2), the combination of predictors: Hb + AST + hs-cTnI + CRP resulted in mean AUROC of 0.789 (mean AUPRC=0.7), Fig. 3.35, Table 6 or slightly worse results compared to model having included Serum Creatinine as predictor were obtained. The mean AUROC score of the model that provides best discrimination ability: Hb + Serum Creatinine + AST + hs-cTnI + CRP forms an elbow point in AUROC scores line plot, Fig. 3.36.

Table 6. Predictive capacity under different models' selection

Combination of predictors	Mean AUROC	Mean AUPRC
Hb + Serum Creatinine + LDL + HDL + Triglycerides + ALT + AST + hs-cTnI + CRP	**0.769**	**0.691**

Hb + Serum Creatinine + LDL + HDL + Triglycerides + AST + hs-cTnI + CRP	**0.776**	**0.698**
Hb + Serum Creatinine + HDL + Triglycerides + AST + hs-cTnI + CRP	**0.78**	**0.702**
Hb + Serum Creatinine + HDL + AST + hs-cTnI + CRP	**0.792**	**0.717**
Hb + Serum Creatinine + AST + hs-cTnI + CRP	**0.805**	**0.712**

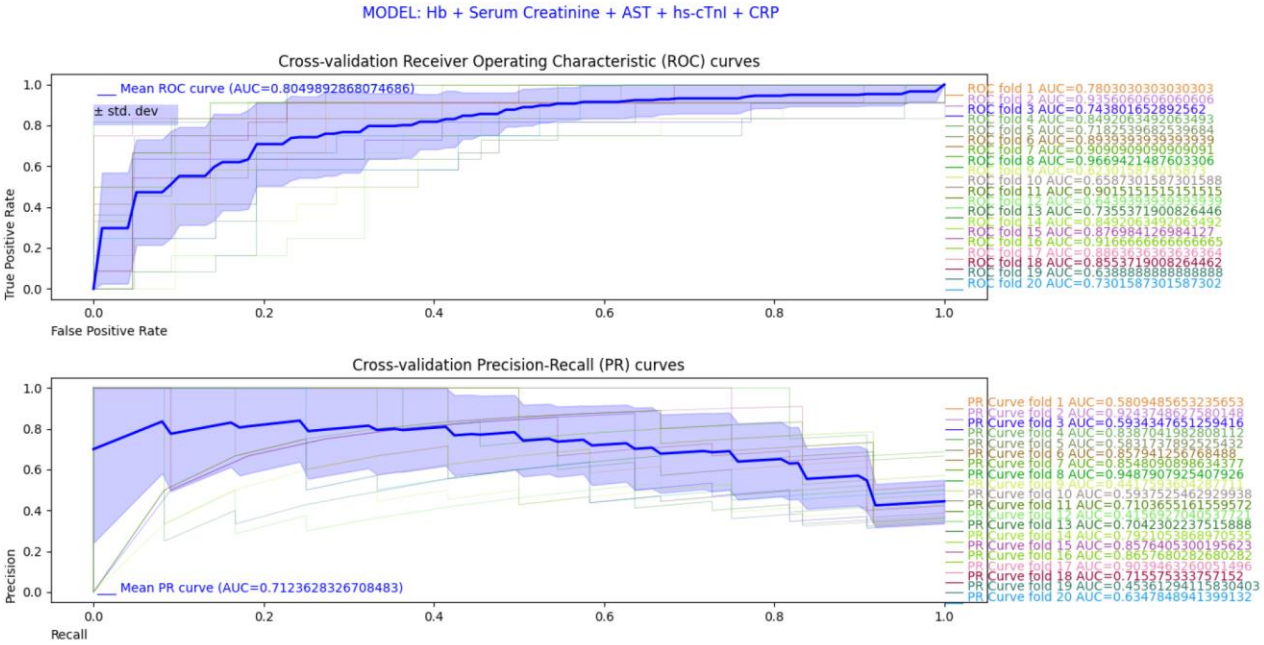

Figure 3.30 Model: Hb + Serum Creatinine + AST + hs-cTnI + CRP

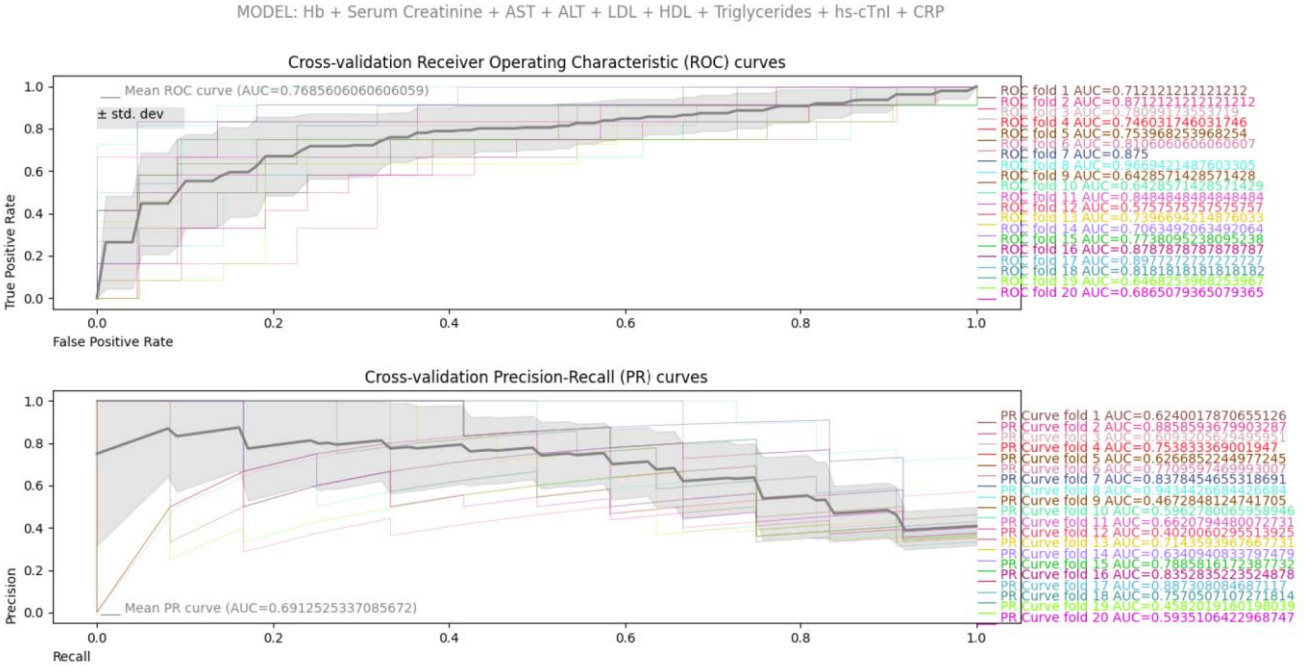

Figure 3.31Model: Hb + Serum Creatinine + AST + ALT + LDL + HDL + Triglycerides + hs-cTnI + CRP

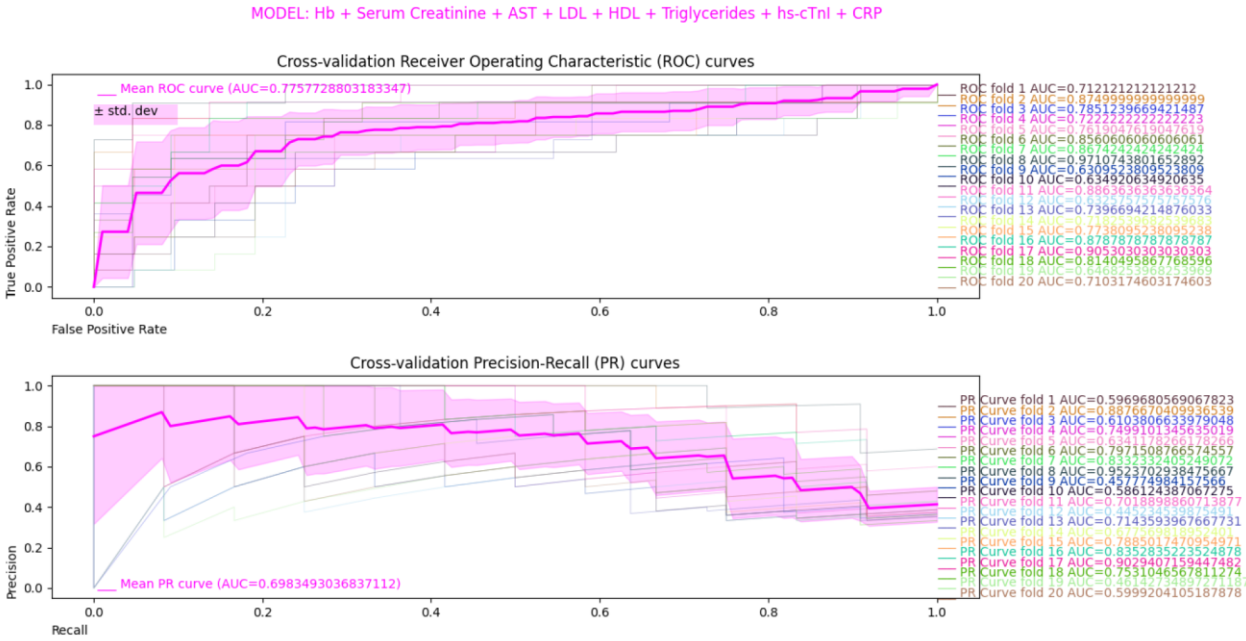

Figure 3.32 Model: Hb + Serum Creatinine + AST + LDL + HDL + Triglycerides + hs-cTnI + CRP

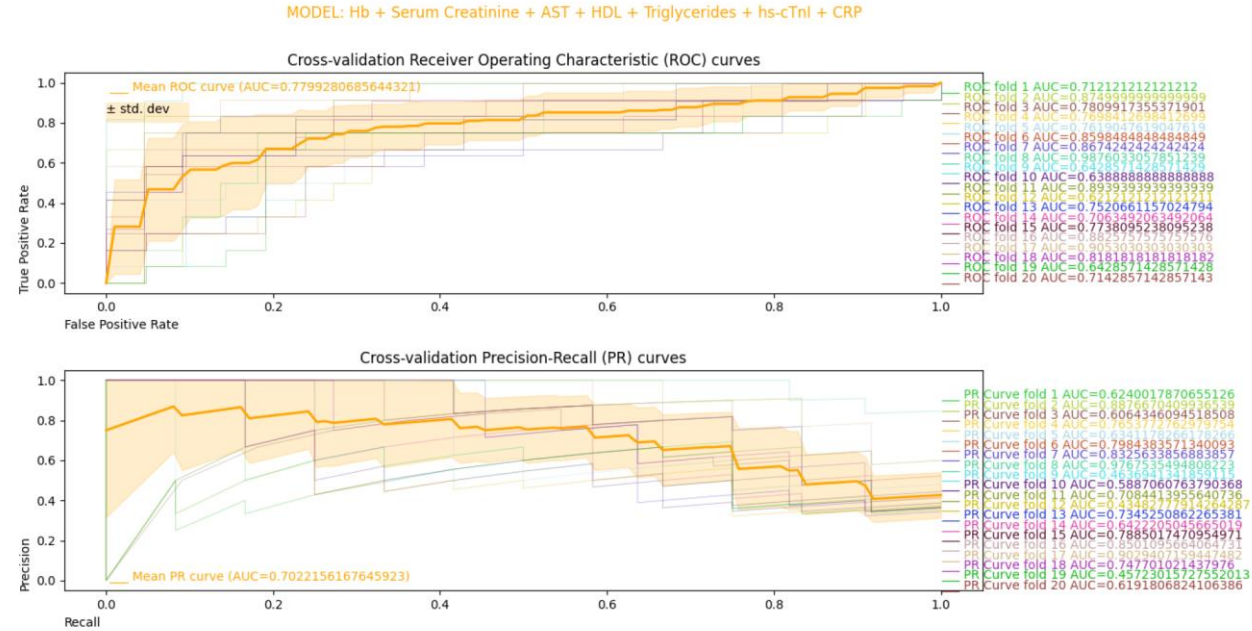

Figure 3.33 Model: Hb + Serum Creatinine + AST + HDL + Triglycerides + hs-cTnI + CRP

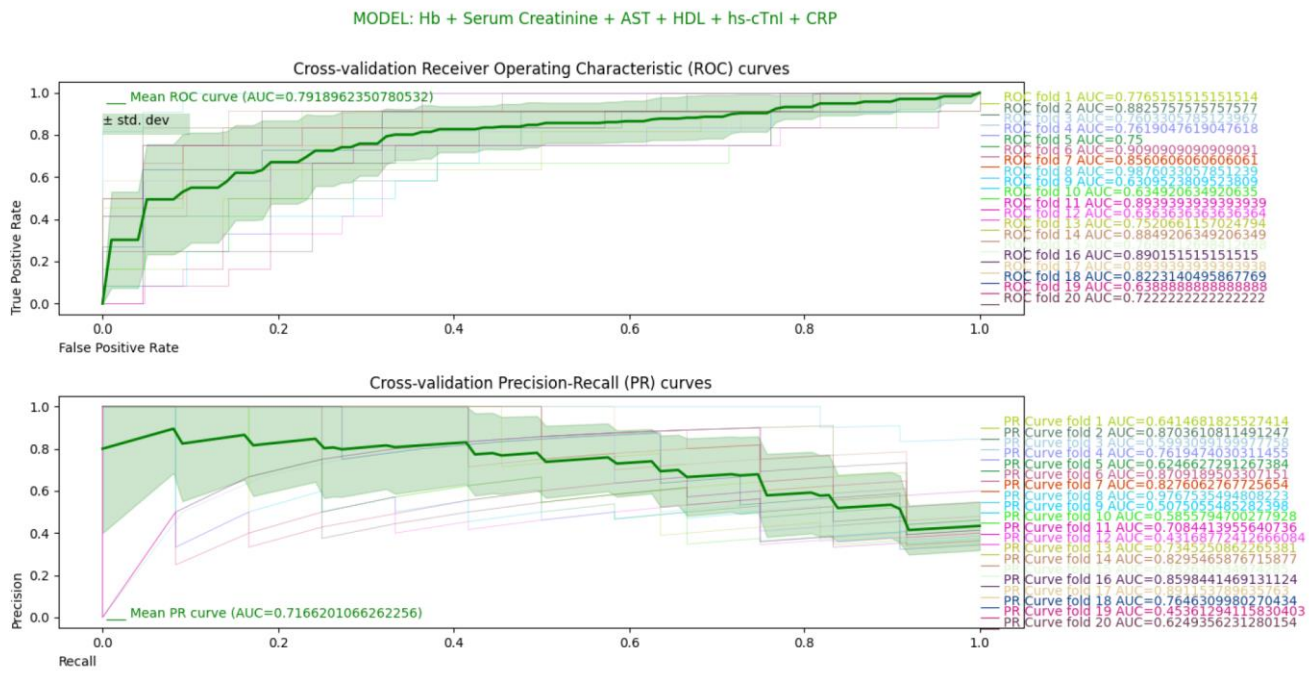

Figure 3.34 Model: Hb + Serum Creatinine + AST + HDL + hs-cTnI + CRP

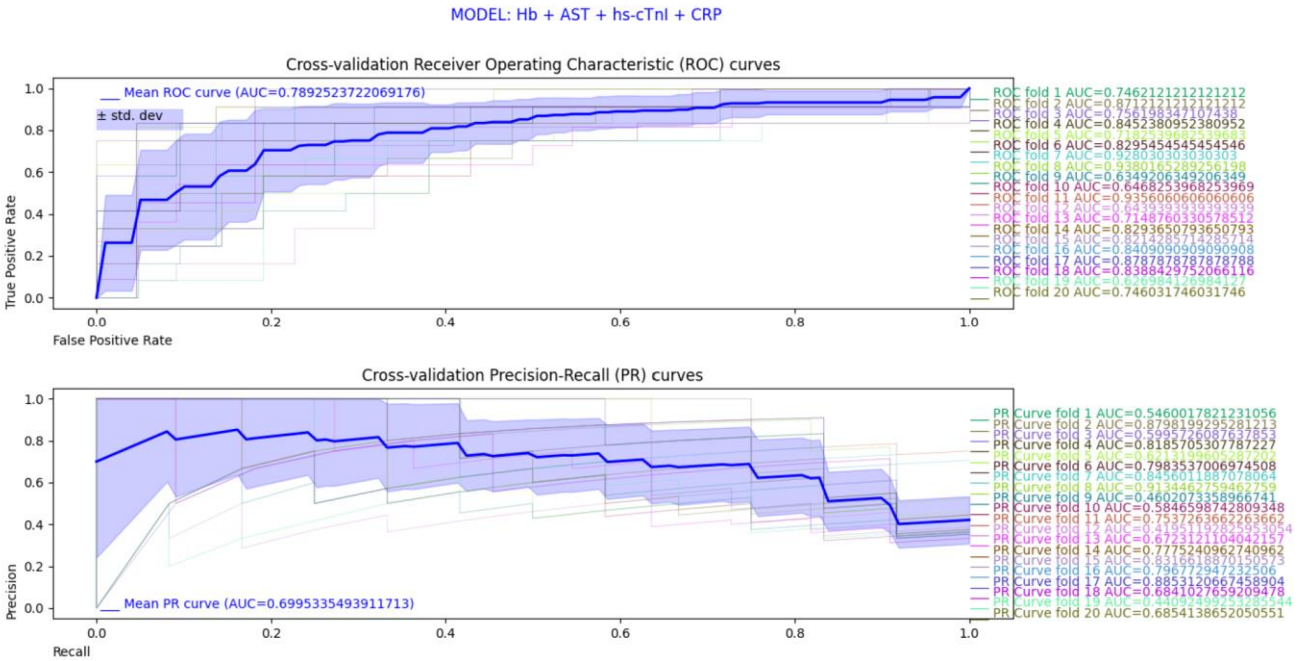

Figure 3.35 Model: Hb + AST + hs-cTnI + CRP

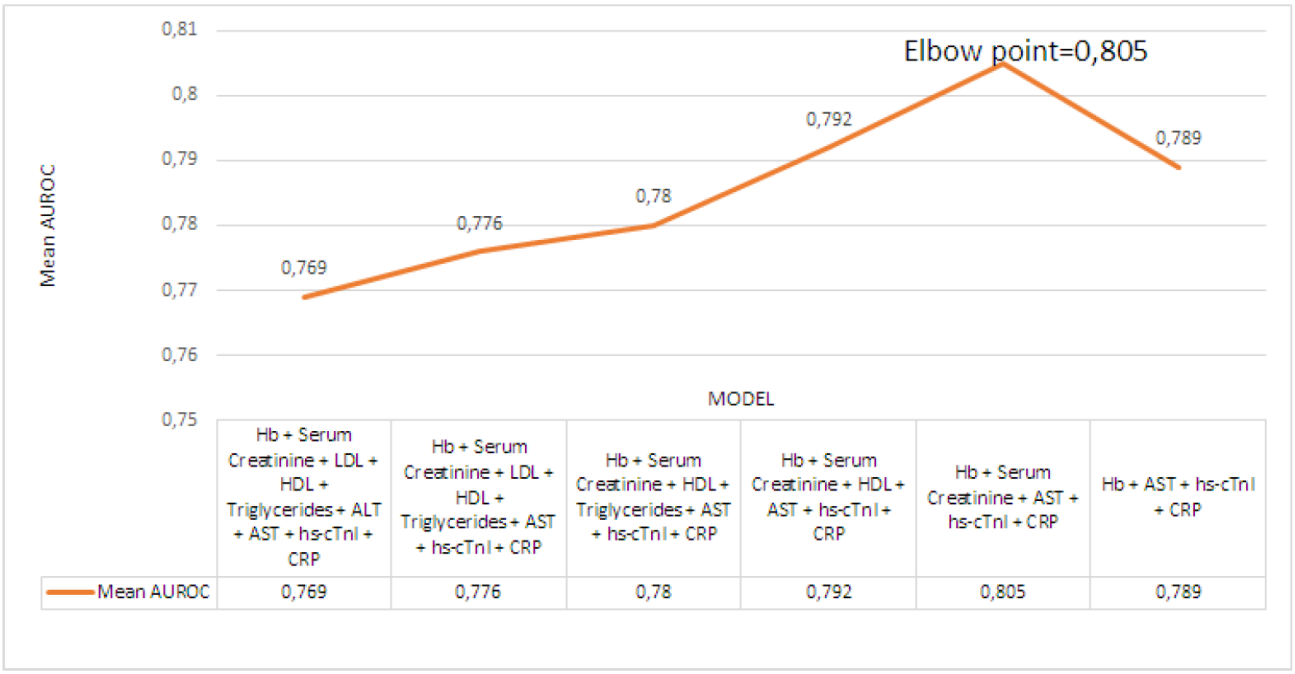

Figure 3.36 Mean AUROC scores line plot

3.3.6 Discussion

The preliminary findings based on logistic regression analysis of 167 CIHD+HF cardiac patients, suggest positive correlation between: AST, ALT, CRP and the outcome of HF against CIHD, and negative correlation between: Hb, HDL and the outcome of HF against CIHD, Table 3. Having included regressor's all data, Serum Creatinine, LDL, Triglycerides and hs-cTnI were not significant as predictors, (p-value>0.05). The basic assumption of logistic regression for linearity between log odds and the outcome CIHD(0)/HF(1) was corrupted in the case of hs-cTnI due to the high percentage of extreme outliers (11.98%) in hs-cTnI distribution, Fig. 3.27. In absence of extreme outliers, hs-cTnI is highly reliable (p-value=0.002) prognostic factor of the outcome of HF against CIHD, such as pg/mL increase of hs-cTnI increases the odds of HF against CIHD for 2.68% on average, Table 4. Since the goodness of fit is primarily affected by particular residuals of high influence $r_i{}^D > 2$ ($r_i{}^D < -2$), highly reliable results were computed, having discarded such residuals out of AST and CRP regression models, Table 5, Fig. 3.29. At p-value=0.000 U/L increase of AST was found to increase the odds of HF against CIHD for 11.34% and mg/L and the increase of CRP was found to increase the odds for 12.4% on average, Table 5. One can say that one-unit increase either in AST or CRP resulted in approximately 12% increased odds of HF against CIHD, Table 5. Model selection plays

pivotal role in ML. Following results in Table 6 (mean AUROC(AUPRC) scores), model's ability to discriminate between HF and CIHD depends of the predictors included in the model. As estimated by the mean AUROC score, removing insignificant predictor improved mean diagnostic capacity, Table 6. The mean diagnostic capacity increased for 0.72 % on average for having removed one insignificant predictor, Table 6. On moderate-sized dataset (167 CIHD+HF cardiac patients), the model: Hb + Serum Creatinine + AST + hs-cTnI + CRP has been identified that provides on average excellent discrimination [104] between HF and CIHD (mean AUROC score=0.805>0.8), Fig. 3.30, Table 6. Our 20-fold cross-validation analysis showed that the model: Hb + Serum Creatinine + AST + hs-cTnI + CRP can assign in 80.5% of the time higher rank to randomly selected HF patient than randomly selected CIHD patient. Three models: Hb + Serum Creatinine + AST + HDL + Triglycerides + hs-cTnI + CRP; Hb + Serum Creatinine + AST + HDL + hs-cTnI + CRP; Hb + Serum Creatinine + AST + hs-cTnI + CRP had acceptable mean diagnostic precision on HF (mean AUPRC score>0.7), Table 6. Off all three, model Hb + Serum Creatinine + AST + HDL + hs-cTnI + CRP had the highest mean AUPRC score of 0.717, Table 6. If the number of patients was higher, the AUROC(AUPRC) score would be higher. Even though Serum Creatinine is insignificant as single predictor (p-value=0.115), its covariance in addition to: Hb, AST, hs-cTnI and CRP positively affects the overall discrimination ability of the model, Table 6, Fig. 8, Fig. 13. Model Hb + AST + hs-cTnI + CRP had mean AUROC(AUPRC) score of 0.789(0.7) compared to 0.805(0.712) for the model Hb + Serum Creatinine + AST + hs-cTnI + CRP, Table 6, Fig. 3.35, Fig. 3.30. Some studies [56], [88][89], investigate ML models for cardiovascular diagnostic on public or freely accessible data. In this study our own data were sourced and ML was applied. Current studies explore different types of parameters as covariates in ML models, such as: demographic [90], [91], biochemical [90], carotid artery ultrasound images[90] and status parameters, such as: smoking or diabetes status [91] [56]. In this study biochemical variables were used. Some biochemical variables, such as: cholesterol, triglycerides [90] [93] are used as covariates in other studies but in addition to parameters that are very different from the parameters that were considered in this study. No study so far has evaluated the joined predictive capacity of biochemical parameters considered here. Studies for cardiovascular diagnostics usually apply ML to discriminate among healthy and diseased individuals, [87]–[89]. Diseased subjects are usually annotated as positive class (1), while non-diseased subjects as negative class (0) and the main purpose of ML model is to discriminate among classes. This study will go a step forward aiming to discriminate between two different cardiovascular diagnoses: CIHD (0), negative class and HF (1), positive class, that has not been addressed so far. As usual practice, different ML models are evaluated in order to identify which model provides best discrimination utility under fixed set of variables of interest [56], [87]. This study aims to select optimal set of

variables for discrimination of HF against CIHD. The problem of selection of near-optimal parameter combination was examined in [105] comparing the performance of Grid Search against Genetic Algorithm for SVM parameter optimization. For the same purpose Logistic Regression was used in this study. Only few studies implement cross-validation as regular model evaluation technique, [87] (10-fold cross-validation)[91] (5-fold crossvalidation). This was done in this study, but for higher number of folds=20 (20-fold crossvalidation). Results at random or optimal cut-off point may be reported if ROC or PR analysis is dismissed. ROC (PR) analysis is provided in: [91], [93] and both characteristics (ROC and PR) are considered in [94]. Since one characteristic analysis (ROC or PR) may provide partial insight towards model's discrimination ability, in this study both characteristics: ROC and PR were examined. In order to increase diagnostic accuracy, some studies apply hyperparameter tuning [89][91]. No parameters were tune and a satisfactory AUROC score was obtained of 0.805 for Hb + Serum Creatinine + AST + hs-cTnI + CRP. Time series in data may undermine model's reliability and only few studies, such as [91], properly address this inquiry, considering the most recent data. If data before and after therapeutic treatment, before and after surgery, before and after lifestyle modification, participates equally in ML model, the model loses its credibility on predictions under specific circumstances. Blood analysis results obtained at hospitalization onset were used in order to tailor predictivity to a specific medical condition or scenario – discriminate HF versus CIHD based on values of specific blood parameters in crucial moments when patients are hospitalized at the cardiac or emergency care unit with serious symptoms. The model that was developed can be used as a direct aid to clinical-decision making and likely help in reducing the time in relation to establish a diagnosis.

3.3.7 Conclusion

In this study the computational capacity of logistic regression has been exploited as a core model for predicting of the outcome of heart failure against chronic-ischemic heart disease in elderly populations. For that reason, data from 167 cardiac patients (108 CIHD and 59 HF), hospitalized at cardiology ward in Villa Scassi hospital have been sourced. Data on 9 biochemical variables were considered: Hb, Serum Creatinine, LDL, HDL, Triglycerides, ALT, AST, hs-cTnI, CRP, onset to hospitalization. Based on comprehensive cross-validation analysis subset of biochemical variables have been identified: Hb + Serum Creatinine + AST + hs-cTnI + CRP that provides excellent discrimination between HF and CIHD. The logistic regression ML model using the combination described above discriminates in 80.5% HF patients against CIHD patients. This is one of the main

contributions of the study, since the: Hb + Serum Creatinine + AST + hs-cTnI + CRP combination is recommend for accurate early detection of the outcome of HF versus CIHD in logistic regression-based model. The predictive potential of each biochemical parameter was also investigated. The computational study that was carried out found that a unit increase of AST, ALT or CRP increases the odds of HF against CIHD for 3.43%, 2.46% and 4.11% respectively, p-value 2 ($r_i{}^D < -2$), AST and CRP goodness of fit dramatically improved after discarding. In such circumstances, one-unit increase of AST or CRP increases the odds of HF against CIHD for approximately 12% on average.

4 Discussion

At the start of the setting up of the HEHRS, the record system of the cardiology wards was completely paper based, but, in connection with the adoption of the REHRS, the staff reckoned that it was necessary to set up an EHR that could be integrated into it, in order to avoid setting up procedures on a paper record first and subsequently converting them to a digital format for the REHRS.

This work has taken into account the specific needs of the cardiology staff as relate to storage stability and responsibility attribution, while retaining the confidence of the staff in the paper-based system, which had been used for many years. The system that has been set up satisfies these needs using the data base systems and the authentication systems of both hospitals. The design features of the EHR guarantee both storage stability and responsibility attribution and for any stored information, the staff member who stored or modified or cancelled can be unidentified. These features have been obtained by an architecture that closely resembles the one in [9] and that is commonly adopted in many EHRs (also commercial) that are being used in many hospitals. An additional need was interoperability with other hospitals and local medical informatics applications, a feature that is present only to a small extent in commercial EHRs [5]. For this reason, it was decided that an EHR would be set up from scratch rather than using already available material. The system modules relating to interoperability are based on HL7 and FHIR standards, as described in the previous sections. With regard to the objectives described in the Introduction section (therapy, referrals and discharge letters), all the commercial systems are already adapted to the first point. For the second and third point, the use of standards has been crucial. Our system is highly efficient compared to other commercial systems.

Information security aspects have not been described in detail because, in accordance with the Italian national and regional legislative constraints, the security management has been completely delegated to the systems that have been set up by the two hospitals and by the regional infrastructure to which they belong (see Appendix A).

Access to personal, sensitive and ultra-sensitive data, which are present in the ad-ministration software, is strictly compliant with national and European Union regulations (such as the General Data Protection Regulation on privacy, n. EU 2016/679 and the European Medical Device Regulation, n. EU 2017/745) for software such as the EHR.

This approach is rather traditional. Relevant innovative work has been recently carried out [106]–[108]; however, in order to apply such approaches, a legislative adjustment would be necessary. This is particularly evident in relation to blockchain systems, in which distributed data storage a typical

feature of this approach is currently strongly countered by public administration data managers in many countries.

5 Conclusions

The development of the CEHRS started at the beginning of 2018, with a very close interaction between software developers and physicians, adopting the main criteria of the agile development methodology, which allows for quick prototyping and constant testing of the system by the users. In December 2018, the CEHRS was adopted formally on an experimental basis, but in essence, it immediately became the only software support of the ward. In October 2020, the experimental phase was completed, the CEHRS was adopted and became the only official health record of the cardiology ward. In May 2021, the CEHRS was also adopted in the cardiology ward of PAM.

In VS, 4093 admissions have been managed so far, among which 3395 patients have been hospitalized (2295 males with average age 70 and 1103 females with average age 76). In PAM, 628 admissions have been managed so far, among which 556 patients have been hospitalized (330 males with average age 73 and 226 females with average age 76).

The CEHRS also supported the cardiology ward in in VS in 2020, when it was de-voted to the treatment of patients with SARS-COV2 for several months. A total of 139 admissions and 139 hospitalized patients have been managed. This has made evident its versatility and flexibility, which enables its use in wards different from cardiology.

The use of CEHRS has enabled the cardiology wards of VS and of PAM to be included in the REHRS. It can, therefore, be concluded that, after a few years of use of CEHRS, the objectives described in the introduction have been met.

In the future, the high analytical capacity of the CEHRS database will enable the secondary use of EHR, both for further clinical studies and for the development of further clinical decision support systems.

Another important contribution of the REHRS to the research domain is improving the efficiency of clinical trials. At present, most clinical trials require the creation of a unique information infrastructure to ensure protocol compliance and to collect essential research data. With the REHRS, every practitioner would have access to a fully functional EHR, so clinical trials could routinely be implemented through the dissemination of guidelines that specify the research protocol. Data collection would occur automatically while administering the protocol, reducing time and costs. In addition, there would be substantial value in analysing, de-identifying and aggregating data from routine patient care to assess the outcomes of various treatments and monitor the health of individuals or groups.

The availability of strongly structured data in connection with natural language in-formation will, on one side, support patient management throughout the diagnostic and therapeutic process also after discharge and for any rehospitalizations, independently of the specific hospital, while, on the other side, it enables its secondary use in anonymous and aggregate formats to support clinical studies.

This will also be favoured by the presence of standardized systems for the management of clinical terminology, which are spreading in Italian regions, and by the continuous adaptation to innovations related to security and interoperability, considering the evolution of legislative constraints.

Specifically, the ability to use all EHR parts based on natural language (anamnesis, clinical diary and hospital discharge letter) for research is very promising. In this respect, the interoperability features of the EHR can interface effectively with terminology management systems [109]–[111] and with natural language processing systems.

Appendix A

The security related rules and guidelines—as for all aspects of the Italian public administration have been set up according to the accessibility technical requirements to technology standardization at the international level and to European Union regulations. They guarantee protection, availability, accessibility, integrity, data confidentiality and operational continuity of systems and of infrastructures.

With respect to information security, all software modules used in the Liguria local health company (which includes the EHR that has been set up) comply with the ICT se-curity minimal requirements for public administrations, which are an integral part of the guidelines for security for Italian public administrations. The guidelines provide a reference to assess whether the protection level provided by an infrastructure responds to operational needs and to identify suitable interventions for its adjustment. The Liguria local health company has aligned with the goal of assuring resilience of its information structure with regard to accidents or hostile actions that might impair the operation of systems and of physical assets controlled by them, equipping itself with standards for prevention and reaction to adverse cybernetic events.

Some examples of such standards are as follows:

- Connection blocking for unauthorized devices and staff;
- Firewall antispam, antimalware, antivirus;
- Internet protocols of any resource connected to the network;
- Authorization and checking of all installed software;
- Dedicated VLAN fractioning;
- Minimal and identified TCP ports opening;
- Backup update procedures and network systems recovery;
- Disaster recovery policies to guarantee operational continuity of particularly sensitive systems;
- Tracking on the operations carried out on local health company software;
- Deactivation of all automatisms that may allow unauthorized access to systems

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