Universitat de Girona
Facultat de Medicina

Evaluating the functioning of a Rapid Diagnostic Unit of patients with Constitutional Syndrome

A retrospective study

CHV CONSORCI HOSPITALARI DE VIC

FINAL DEGREE PROJECT

AUTHOR: Isabel Depoorter Ruelle
CLINICAL TUTOR: Dr. Xavier Pla Salas
METHODOLOGICAL TUTOR: Dr. Xavier Castells

January 2018

Acknowledgments

This project has been a challenge due to the novelty of the field of research. However, everything I've learnt brought me a great personal satisfaction. None of this would have been possible without the following persons, whom I want to express my acknowledgments:

I would like to thank first and foremost my tutor Dr. Xavi Pla Salas. He made me feel welcome every day of my internship at the Day Care Hospital, as well as teaching me as much as he could. Even if the Day care hospital was extremely crowded, he was always predisposed to help me. His willingness and entrepreneurial attitude has guided me throughout these 4 months, and actually, I am pretty sure it will guide me in my career as a doctor in the near future. Thank you for always having faith in me, I just could not ask for more.

I would also like to thank Marc Saez for his help along this final degree project. Thank you for solving all my doubts over the statistical part, and for always being there for your students.

Thanks also to my methodological tutor Xavier Castells for helping me with the methodological part of the study.

Thanks to my parents and friends for being always by my side.

To conclude, I want to express my deep gratitude to the persons mentioned above and to everyone around me for the great encouragement you have given to me!

INDEX

FIGURES INDEX

TABLES INDEX

1. ABSTRACT

BACKGROUND: Constitutional syndrome (CS) is a group of non-specific symptoms (asthenia, anorexia and involuntary weight loss) frequently found in the setting of a wide range of diseases, amongst which cancer is the most important. Those in charge of carrying out the diagnostic approach of patients with CS are the Rapid diagnostic units. This unit's main objectives are to reduce diagnostic delays at the same time of preventing unnecessary admission, since they are ambulatory care units.

PURPOSE: To evaluate the functioning of the Rapid diagnostic unit of Hospital Universitari de Vic in terms of agility and rapidity of the CS evaluation and detect alterations in order to improve them. And to know the frequency of the diseases responsible for the constitutional syndrome.

METHODS: We analysed the medical history of all the patients with constitutional syndrome attended at the Rapid Diagnostic Unit in two years (from May 2015 to April 2017).

RESULTS: a total of 88 patients were referred to the unit from different health facilities (specially from primary health care and emergency department). The unit took a median of 3 days to visit patients with CS since they were referred and a median of 3 more days to achieve the diagnosis. The median time to get complementary tests performed and the medical report obtained was 5,5 days. The most frequent cause of CS was cancer (37,5% of all the diagnosis), followed by psychiatric diseases (22,7% of all the diagnosis). The most frequent type of cancer were the digestive neoplasms, and amongst all the cancer, 60,6% presented metastasis at the moment of the diagnosis.

CONCLUSION: The rapid diagnostic unit of Hospital Universitari de Vic is efficient in speeding up the diagnostic process of patients with CS. In the case of potentially serious diseases, as cancer, the unit has the agility to accelerate the diagnostic procedures as much as possible, so the best therapeutic approach can be conducted in these patients. The most common diseases responsible for constitutional syndrome were malignant neoplasms, which most of them had already advanced stages. Cancer was followed, in decreasing frequency, by psychiatric disorders and organic but non-neoplastic diseases as digestive diseases.

2. ABBREVIATIONS

CS	Constitutional syndrome
CSUA	Constitutional syndrome of unknown aetiology
DCH	Day care hospital
DoH	Declaration of Helsinki
ED	Emergency department
FDP	Final degree Project
FORES	*Fundació d'Osona per a la Recerca i l'Educació Sanitària*
GDS	Geriatric depression scale
HGG	Hospital General de Granollers
HIC	Hospital inpatient care
HIV	Human immunodeficiency virus
HUV	Hospital Universitari de Vic
ICU	Intensive care unit
IMS	Internal medicine service
IQR	Interquartile range
IWL	Involuntary weight loss
OCF	Outpatient care facility
PHC	Primary health care
RDU	Rapid Diagnostic Unit
REC	Research ethics committee
SD	Standard deviation
SICHV	*Sistema d'Informació del Consorci Hospitalari de Vic*
WMA	World Medical Association

3. INTRODUCTION

3.1 CONSTITUTIONAL SYNDROME

Constitutional syndrome (CS) is the association of asthenia, anorexia and significant weight loss (1). Weight loss is understood as an involuntary decrease of 5% of total body weight in 6 months (2,3).

There's no uniformity when it comes to referring to this entity. There are different concepts in the literature to define it, such as *general syndrome*, *cachexia-anorexia-asthenia syndrome* or *cachectic syndrome* (4).

Detecting the underlying cause of CS has been a clinical challenge for professionals because of its varying presentation and manifold aetiologies. For this reason, sometimes a thorough evaluation is needed. Usually, the three main manifestations coexist, but sometimes the patient has only one or two of them.

Some nonspecific symptomology is usually associated to CS: low-grade fever, headache, myalgias or diaphoresis. If after an anamnesis and a complete exploration, it hasn't been possible to orient the process toward a specific aetiology, we talk about solitaire constitutional syndrome.

3.1.1 COMPONENTS OF CONSTITUTIONAL SYNDROME

- **Asthenia** (1,5,6)**:**

It's the subtlest CS manifestation. This complex symptom simultaneously covers the physical and mental processes in a global way, it is subjective and implies a set of vague feelings, different for each individual.

Patients use different expressions to describe how they feel, so it's important to pay attention and distinguish situations which can confuse the clinician. For example, some refer to be fatigued, but from a physiological point of view, fatigue occurs after the effort, and asthenia as the same feeling, but without efforts to justify it. Terms like weakness (identifiable as fading, dizziness or unsteadiness) or dyspnoea may be misunderstood by patients.

Differences between organic and functional asthenia lie in its aetiology, duration, tolerance exercise, fluctuating course and symptomatology:

- *Organic asthenia*: associated with chronic somatic diseases or progressive organic pathology. It usually lasts less than functional asthenia and its symptomatology is often better defined.
- *Functional asthenia:* associated with temporary reversible condition. It's also called reactive, as in fact is the body's response to stressful situations. It may fluctuate or be intermittent, being worse defined than organic asthenia. If asthenia is an isolated symptom, its origin will generally be functional.

- **Involuntary weight loss (IWL):**

Clinically important weight loss is defined as the loss of 4,5 kg or more than 5 percent of usual body weight over a period of 6-12 months (7). This definition is also applicable to IWL in overweight people or obesity.

By weight loss, we generally understand loss of fatty tissue, without referring to the loss of lean tissue or water. However, on the whole, weight loss greater than 10% is considered to represent protein-energy malnutrition, which is associated with impaired physiologic function such as impaired cell-mediated and humoral immunity. Weight loss in excess of 20% implies severe protein-energy malnutrition and is associated with pronounced organ dysfunction (2).

Therefore, unintentional weight loss may reflect disease severity or undiagnosed illness. Some studies verify that important weight loss (4-5% or more of body weight within 1 year, or 10% or more over 5-10 years or longer) is associated with increased mortality and morbidity (2,8).

The aetiologies of weight loss are reflected in **Annex 1**. Although studies have different methodologies, some common key concepts emerge from most series: among organic aetiologies, cancer is the most common; the aetiology of weight loss is evident without an extensive evaluation in most patients; and psychiatric illness and non-diagnostic evaluations are common.

- **Anorexia:**

Anorexia itself means decreased appetite (9). Alterations in appetite occur in a wide variety of organic and functional diseases. However, physiologically, elderly persons experience a linear decrease in food intake over the life span. This is explained by decreased physical activity and altered metabolism with aging. Thus, older people fail to adequately regulate food intake and develop a physiologic anorexia of aging. This physiological process of anorexia depends not only on decreased hedonic qualities of feeding with aging but also hormonal and neurotransmitter regulation of food intake. Despite of developing anorexia, they normally increase body fat and obesity.

Even if anorexia of aging is categorised as physiological, it may be a major contributing factor to under-nutrition and adverse health outcomes in the geriatric population. It's recognized as an independent predictor of morbidity and mortality (10).

In turn, not all appetite decreases in elderly persons should be assigned to life span, since there are a wide variety of organic and functional diseases responsible for loss of appetite.

But in the general population, not only focusing in elderly community, anorexia usually comes along with weight loss, and both are common in chronic diseases. Furthermore, it is common to progressively lead to situations of cachexia or starvation, and even further, if it doesn't revert it can occasionally lead to death.

- ***Cachexia:***

Cachexia usually relates important weight loss, anorexia and other symptoms. A definition emerged from a scientists and clinicians meeting in Washington DC on December, 2006: *cachexia is a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass* (11). Anorexia, inflammation, insulin resistance and increased muscle protein breakdown are frequently associated with wasting disease. Clinically, it manifests in the setting of ongoing disease, usually with disproportionate muscle wasting. Diagnostic criteria for cachexia are exposed in **table 1**.

Table 1. Diagnostic criteria for wasting disease (cachexia) in adults. Adapted from Evans et al (11):

Weight loss of at least 5%[1] in 12 months or less in the presence of underlying illness[2], PLUS THREE of the following criteria: - Decreased muscle strength - Fatigue[3] - Anorexia[4] - Low fat-free mass index - Abnormal biochemistry a) Increased inflammatory markers CRP (>5.0 mg/l), IL-6 (>4.0 pg/ml) b) Anaemia (<12 g/dl) c) Low serum albumin (<3.2 g/dl)
The following needs to be excluded: starvation, malabsorption, primary depression, hyperthyroidism and age-related loss of muscles mass. 1. Oedema-free. 2. In cases where weight loss cannot be documented a Body Mass Index < 20.00 kg/m² is sufficient. 3. Fatigue is defined as physical and/or mental weariness resulting from exertion; an inability to continue exercise at the same intensity with a resultant deterioration in performance. 4. Limited food intake

Cachexia is a frequent process in patients with cancer, especially in advanced stages. The pathogenesis of cachexia in cancer is attributed to factors related to the host or tumour(12). The ones related to the host may be a humoral response (generated as the guest's biological response to the presence of the tumour: activation of TNF-α production and several interleukins) or be related to the treatment (chemotherapy, radiotherapy or surgery). Factors related to the tumour are produced by the tumour itself, and the best known are the proteolysis-inducing factor (PIF) and the lipid mobilizing factor.

In these patients, digestive disturbances secondary to the tumour growth, such as dysphagia, odynophagia, persistent constipation or dysgeusia, may contribute to the cachexia process, and coexist with humoral or tumour factors (12).

3.1.2 EPIDEMIOLOGY

Epidemiological data about CS depends on the characteristics of the studied population, the care level where patients are received, and the clinical manifestations required as members of this syndrome.

Thus, the presence of the three main clinical manifestations (anorexia, asthenia and weight loss) differ from 3,4% of the patients seen in an internal medicine service (13) to 11% in another internal medicine service from another hospital (14). Differently, isolated weight loss is present in 15-20% of elderly patients (8) in clinical practice, and this percentage increases to 50-65% in nursing home residents.

When it comes to cachexia, more specifically in cancer cachexia, its prevalence varies from 40% of the patients in the diagnosis phase to 70-80% in advanced stages. The prevalence of cancer cachexia also varies according to the origin of the primary tumour: 83-85% in pancreatic and gastric neoplasm; 54-60% in lung, prostate and colon neoplasm and, 32-48% in mama neoplasia, sarcoma, lymphoma and leukaemia (12). Life expectancy in oncological patients with cachexia is significantly lower than those who do not present it (15). Furthermore, it can be the direct cause of death in more than 20% of these patients.

3.1.3 AETIOLOGY

There is a wide range of entities which can cause constitutional syndrome.

- **Psychiatric illnesses:**

  Psychiatric entities are frequent causes of CS, and they usually go unnoticed, thereby the importance of an exhaustive anamnesis. Some of the related diseases are depression, eating disorders, dementia, somatization disorders or anxiety.

  Depression is the most common entity and its frequency increases among elderly patients (4). Its presentation is often hidden, not clear, and the diagnose may be undetected.

  Different assessment scales are available for an initial screening. The most well-known is Geriatric Depression Scale (GDS), first created by Yesavage et al. and it consists of 30 questions, which patients responds yes or no about how they have felt on the day of administration. A shorter and simpler version of the GDS was created from the original one, and it is made up by 15 questions (**Annex 2**). Its efficacy is as good as the full 30-item and it is now widely used as a screening for depression in older adults. The grid sets a range of 0-4 as “normal”, 5-8 as “mildly depressed”, 9-11 as “moderately severe” and 12-15 as “severely depressed”.

  When depression is the main reason for the CS, all the patients improve their symptoms with the treatment. However, some reactive depression to neoplasia have been described, as pancreatic cancer, so it is convenient to remain vigilant (16). Patients who are diagnosed with pancreatic cancer tend to present more easily depressing symptoms than other cancer groups (17). One of the most recent studies showed up to 56% of patients with mean depression and pancreatic cancer (18). Depression may even precede the diagnosis of pancreatic cancer (19,20). Thus, even if depression is the cause of CS, it is convenient to remain vigilant, because the diagnosis of a depression may not rule out the diagnosis of a concomitant malignant neoplasia.

- **Tumour diseases**

  Tumours are the general cause of CS. Almost all cases are secondary to malignant neoplasms, and only 5% are due to benign tumours (4). Some reviews determine that 10% of malignant tumours

are already locally advanced diseases at diagnosis, and more than 50% present distant metastases when CS is present. Here we see the situation when cancer cachexia and constitutional syndrome are used as synonyms. Because of its poor prognosis in oncological patients, it should be suitable to consider that after all CS lies a neoplasm until the opposite is not demonstrated.

According to different studies (4,12,13,21), more than half of tumours causing CS are gastrointestinal. Of these digestive cancers, the most frequent, in order of frequency, are pancreatic and gastric tumour, followed in a certain distance, by colorectal and hepatic tumours.

The following tumours in frequency are disseminated tumours of unknown origin, generally in form of liver or bone metastasis (4,22). Finally, the least common cancers found in patients with cachexia are genitourinary: and hematologic neoplasms.

Breast or lung cancer have a high prevalence in general population, but patients are already diagnosed of this type of cancer when CS appears.

- **Non-neoplastic gastroenterological disorders**

Gastroenterological disorders are the most common non-malignant organic aetiologies identified in patients with CS. The most frequent of them is peptic ulcer disease (2,13). Other entities described in the medical literature are inflammatory bowel disease, chronic liver disease, mesenteric ischemia, and gastritis. Dysmotility syndromes, celiac disease, constipation, oral problems (periodontal disease, and xerostomia) are less frequent diseases responsible of CS.

- **Autoimmune disease**

Within the autoimmune processes causing CS, we mostly find giant cell arteritis, sarcoidosis, connective tissue disease and systemic vasculitis.

Giant cell arteritis is the most frequent and CS normally appears in early stages of the illness (13).

- **Infectious diseases**

CS normally appears in a chronic or subacute course of infections. Tuberculosis, fungal disease, parasites, subacute bacterial endocarditis, HIV, abscesses and other hidden infection may cause CS.

During the anamnesis, presence of risk factors (recent travels, occupation, lifestyle and history of exposure) or certain symptoms (fever, low-grade fever or dysthermia) can make us suspect an infectious process and consequently, serological and microbiological studies must be done to rule out any infection.

- **Hematologic disease**

Hematologic diseases are only a small proportion of the diagnoses which can cause CS. The most frequent haematological cause is megaloblastic anaemia (4), and other causes are myelodysplastic syndromes or multiple myeloma.

- **Another aetiologies of CS.**

Finally, there are infrequent CS cases associated to other diseases, such as neuroendocrine diseases (hyperthyroidism and hypothyroidism), neuropathies or renal diseases (nephrotic syndrome or uraemia).

Among neurological entities which can cause CS, Parkinson's disease and some degenerative dementia should be mentioned, due to the increased proportion of elderly people in our society.

Some drugs can be responsible of certain CS manifestation (particularly anorexia and weight loss), especially in elderly patients who take lots of medication. Some drugs should be noted (**Table 2**), such as digoxin, acetylsalicylic acid (ASA) or better known as aspirin, angiotensin-converting-enzyme inhibitor (ACE inhibitor), statins and diuretics.

Table 2. Drugs that can be associated to CS (21)

Cardiovascular medication
Digoxin
ASA
ACE inhibitor
CCB
Diuretics (thiazides, potassium-sparing diuretics, loop diuretic…)
Statins
Psychiatric medication
SSRIs
Neuroleptics
Benzodiazepines
Levodopa
Acetylcholinesterase inhibitor
Memantine
Analgesic medication
Opioids
Miscellany
Metformin
Levothyroxine
Antibiotics
Anticholinergics
Iron supplements
Bisphosphonates
Other NSAIDs different of ASA

ASA: acetylsalicylic acid; **ACE inhibitor**: angiotensin-converting-enzyme inhibitor; **CCB**: calcium channel blockers; **SSRIs**: selective serotonin reuptake inhibitors; **NSAIDs**: Nonsteroidal anti-inflammatory drug.

- **CS of unknown aetiology**

In those patients whom a diagnosis was not obtained after an exhaustive research, it is categorized as constitutional syndrome of unknown aetiology (CSUA). These patients must be followed up along a prudential time, to ensure that no new symptoms appear, which might lead to the diagnosis.

CSUA proportion is different among studies (8,13,23,24). The proportion varies from 6,1% to 25% depending on the duration of the following-up and the methodology used by the researchers.

3.1.4 DIAGNOSTIC APPROACH

The main goal facing a patient with CS is to find and treat the underlying cause. Considering all the potential causes, cancer is the major concern, for both patients and physicians. Therefore, the main purpose is to differentiate serious or malignant organic diseases, from which do not have an organic basis.

There is not endorsed clinical guidelines about how to handle CS, but some reviews suggested diagnosis algorithm based in three basic pillars: medical history, physical exploration and diagnostic studies (4,25,26). **Figure 1** shows a general diagnostic algorithm of CS. Anyhow, it's recommended to realize an individual approach, adapting each patient according to their accompanying symptoms, morbidity, functional impact and their expectation and lifespan.

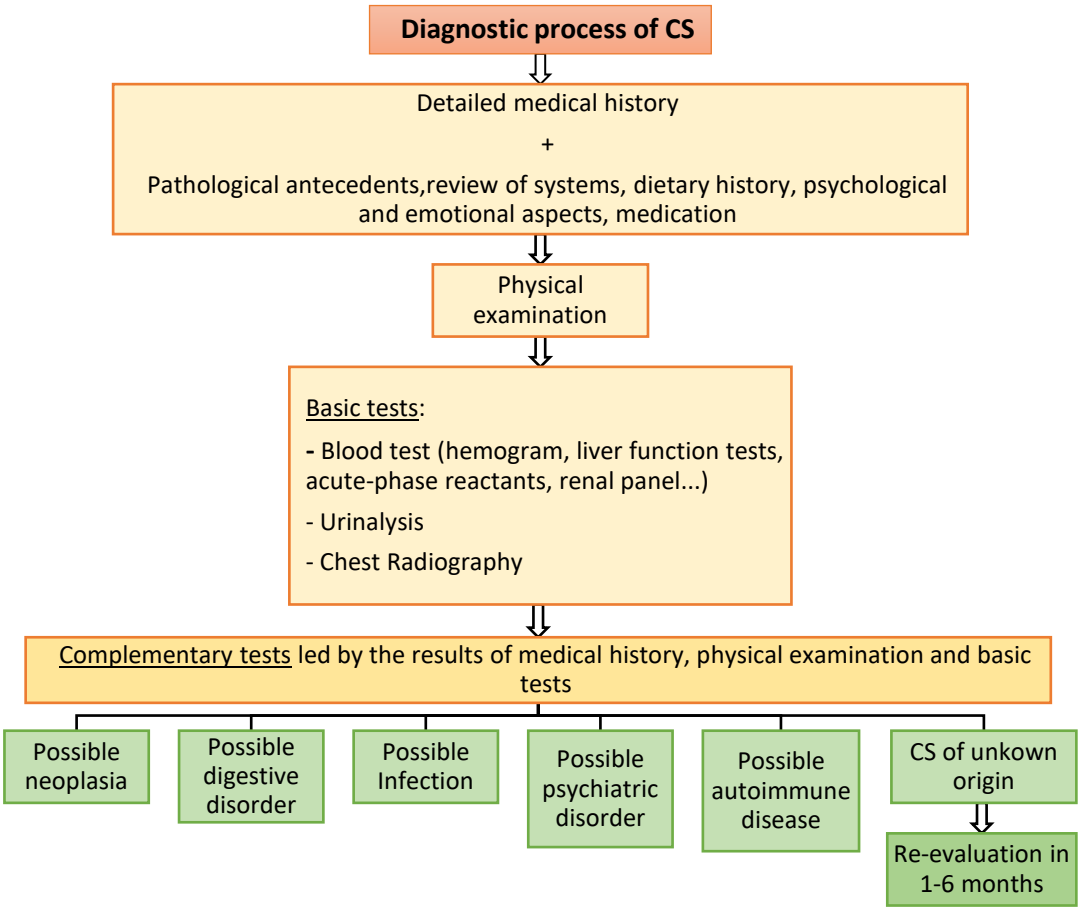


Figure 1. Diagnostic approach of CS. Adapted from Castro et al. (21)

3.2 RAPID DIAGNOSTIC UNIT IN INTERNAL MEDICINE

In the past few years, with the intention of improving and accelerating situations of difficult diagnosis, rapid diagnostic unit (RDU) has been created. RDUs are ambulatory care units which rely mainly on internal medicine service (IMS). They are focused on studying patients with suspected severe illnesses (27).

Its main purpose is to reduce diagnostic delays, improve coordination with Primary Health Care (PHC), optimize diagnostic resources, and moreover, reduce hospital admissions (specifically unnecessary admissions) (28).

RDU functioning is based on offering an immediate first appointment, as well as, giving priority in performing tests to those who need it. An optimal coordination among professionals who are involved in the care process is needed.

In addition, it is necessary the patient and his/her guardians are aware of the ambulatory care system and his/her health condition or family support do not prevent the repeated travels to the hospital.

Reasons for referral use to coincide among RDU of different hospitals and 70% of the cases are: constitutional syndrome, abdominal pain, anaemia, lymphadenopathies, palpable growth, haemoptysis, rectal bleeding or febrile syndrome. Malignant diseases are a frequent diagnose in RDU, followed by digestive diseases (14,27). The suspicion of cancer requires to expedite the diagnostic studies to confirm the diagnosis as soon as possible, due to its severity, prognosis and psychological repercussions. To this effect, a coordinated assistance to these patients is necessary via RDU in order to reduce diagnostic delays.

Furthermore, RDU makes possible to reduce inappropriate hospital admissions, or decrease the duration of hospitalisation. Thus, this results in significant cost savings for the hospital (14).

3.3 RDU OF THE HOSPITAL UNIVERSITARI DE VIC

The RDU of Hospital Universitari de Vic (HUV) was created in 2015 by the IMS of the hospital itself. It was launched at the same time as the new Day Care Hospital (DCH), and both are managed by the same medical team. The opening hours for RDU patients are Monday to Friday from 8 am to 3 pm. The medical team is formed by 3 internal medicine specialists (two of them work full-time and one part-time) and 2 nurses (one works full-time and one part-time), and they cover both the RDU and the DCH. Actually, these medical devises were initiated by a single physician, and over the first 2 years, it was necessary to extend the medical team.

The medical device where the DCH and the RDU are settled, is formed by nine separated spaces of medical attention: six armchairs with chairs for the accompanists, two beds in two separated rooms and a medical consultation that provides major intimacy to the patient when it is interrogated and explored.

Patients who arrive to this RDU normally come from emergency department (ED), outpatient care facilities (OCF), hospital inpatient care (HIC) or primary health care (PHC). Requests for consultation are via telephone and e-mail.

An e-mail was specially created for PHC physicians, so they can make a query or request for consultation to the RDU. The RDU medical team is committed to responding to e-mails in less than 24 hours. ED, HIC and OCF can make informatic referrals via the hospital software.

The most frequent reasons of consultation in this RDU are constitutional syndrome, anaemia, febrile syndrome, systemic autoimmune disease, dyspnoea and lymphadenopathies.

The programming, both the first visit as the successive ones and the diagnostic tests, is carried out concertedly and with preferential character.

If necessary, RDU of HUV can provide intravenous medical treatments and diagnostic procedures (thoracentesis, paracentesis, lumbar puncture, fine needle aspiration cytology of lymphadenopathies or palpable superficial masses…) since the first visit to the patient, which allow a major therapeutic and quick comfort for him/her. There is also the ease of transporting the patient to the radiology services if any medical imaging is needed.

Hence, RDU of HUV summarizes its versatility in the following features:

- Schedule flexibility and ability to adapt to priority requests.
- Possibility of visiting repeatedly the patient, if needed.
- Fluid and quick contact with other specialities.
- Frequent and priority contact with PHC.
- Possibility of hospital admissions if the patient's conditions requires it.
- Availability of the hospital services for whatever is needed (intensive care units – ICU –, pharmacy services, other specialities, medical imaging devices, endoscopic examination…).

4. JUSTIFICATION

The main objective when facing a patient with CS is to find and treat the underlying cause. Cancer frequency as a cause of CS may vary from study to study due to different methodologies or studied population. Certain studies just discuss involuntary weight loss, which is the main symptom of CS, but they do not analyse the complete CS (23). Some others described solitaire CS cases, which means these cases presented just the three symptoms of CS (asthenia, anorexia and weight loss), without any accompanying symptoms (pain, dyspnoea, diarrhoea…) (13). Regarding the populations that have been studied, some studies focused on older people, meanwhile others included adult population globally (29). Anyhow, cancer may not be always the most frequent cause according to the study, but it has a strong influence on the incidence of it.

Bearing in mind all the potential causes, cancer is a major concern for both patients and doctors, because of its poor prognosis in these cases. For this reason, any approach to patients with CS must be addressed to rule out any subjacent neoplasia or any other serious diseases as soon as possible. Those in charge of carrying out this task are the RDU, as is the case of the RDU of the Day Care Hospital of Hospital Universitari de Vic. HUV serves the region of Osona, with 160.000 habitants, and its RDU has been running for more than two years.

To this day, within the medical literature, on the one hand, there are descriptive studies that value the incidence of the different aetiologies of CS, and on the other hand, studies that evaluate the functioning of the RDU in a global way, including all reasons of referral (anaemia, febrile syndrome, systemic autoimmune disease, dyspnoea, lymphadenopathies…). However, no studies have specially assessed the functioning of a RDU in relation to CS, and CS is precisely one of the most frequent reasons for consultation in RDUs (14,30). For this reason, taking advantage of the fact that the RDU of HUV started in 2015, we have considered conducting a specific evaluation of CS in its service.

This study aims to measure the effectiveness of the RDU of HUV in terms of agility and rapidity of the CS evaluation, including an analysis of the procedures used (first and consecutive medical appointments, medical tests…) for getting a correct diagnosis and the delays that have been in the process.

The good functioning of the RDU not only depends on itself, but also on other professionals of the health system, such as health primary care specialists, radiology specialists, gastroenterology specialists, etc. Good coordination is crucial among all these professionals to reach the final goal and be successful.

This study may help to detect alterations in the functioning of the RDU which could decrease either its efficiency, diagnostic rapidity or quality of care. It may allow specialists to strengthen their weaknesses, and consequently, improve the detection of cancer or serious diseases amongst their patients. It will enable to know the diagnostic delays depending on the pathologies, so that an objective analysis could be done on them.

Thus, for the benefit of patients and with a spirit of progress, realizing this assessment can contribute to an

improvement in the care quality, as well as adding epidemiological knowledge to Constitutional Syndrome in Osona region.

5. HYPOTHESIS

- Rapid Diagnostic Unit of constitutional syndrome of Hospital Universitari de Vic is useful and effective in speeding up and getting the final diagnosis.
- Main underlying causes of Constitutional Syndrome from Osona region do not differ from those presented in other studies: cancer as the most frequent organic cause and depressive disorder as the most frequent non-organic cause.
- The most used test is computed tomography scan, both to rule out and to confirm organic pathology.
- Patients with constitutional syndrome who end up with a cancer diagnosis have a particularly poor prognosis in more than 50% of cases.
- Experienced professionals usually have a reliable clinical impression of the patient during the first appointment.

6. OBJECTIVES

The **main objectives** of this study are:

- To evaluate the functioning of the RDU of Hospital Universitari de Vic in relation to constitutional syndrome.
- To detect operating weaknesses to find a way to improve them.

The **secondary objectives** of this study are:

- To know the diseases responsible for the constitutional syndrome in the region of Osona.
- To establish the most used and the most useful diagnostic test to get the diagnosis of constitutional syndrome.
- To elucidate the prognosis of patients with constitutional syndrome who end up with a cancer diagnosis.

7. METHODOLOGY

- STUDY DESIGN

This study is a descriptive, observational and retrospective study performed in patients with constitutional syndrome attended by the Rapid Diagnostic Unit of the Day Care Hospital, in Hospital Universitari de Vic.

- POPULATION IN STUDY

This study focuses on patients with constitutional syndrome referred to the Rapid Diagnostic Unit of the Day care Hospital of HUV from May 1st, 2015 to April 31st, 2017.

- SAMPLE

Sample selection and size

The method of sample selection has been consecutive non-probabilistic. The sampling has consisted in collecting all patients presenting constitutional syndrome who have been attended by the RDU of HUV.

Therefore, the sample size corresponds to all the patients (N) who have been derived and cared by this RDU between the established dates. The final size of the sample is made of 88 patients.

Statistical power

Accepting a significance level (α) set to 5%, and a sample size of 88 patients, maximum indeterminacy, the statistical power of our study is 77,76% (in a two-tailed test) to recognize differences from 10%. It has been calculated by Marc Saez's program, which is inspired in pwr package of the free statistical environment R (version 3.4.2).

- INCLUSION CRITERIA

- Patients referred to the RDU for presenting constitutional syndrome between May 1st, 2015 and April 31st, 2017.
- As constitutional syndrome we assume the presence of asthenia, anorexia and a weight loss above 5% of body weight in the last 6 months. The simultaneous presence of the three clinical features is not strictly necessary. Weight loss has been accepted if it was documented in the medical history, both by numerical estimation of the lost weight (kg), by proportion (>5% of body weight in the last 6 months) or by acknowledgment of a relative or friend.
- The patient has had to be referred from PHC, ED, HIC or OCF of the HUV. The consultation has had to be requested by telephone, electronic mail or internal referrals from ED, HIC or OCF.

- EXCLUSION CRITERIA

- Patients with CS who were referred to the RDU but already having a previous diagnosis of some disease that can cause CS.
- Patients who were voluntarily losing weight by slimming diets or intense physical exercise.
- Patients who were candidates to enter into specific rapid diagnostic circuits of other specialities, like breast cancer RDC, colon cancer RDC or lung cancer RDC.

- DATA

Data collection was carried out through the medical history of the patients, which are electronically-stored in the informatic system of HUV (*Sistema d'informació del Consorci Hospitalari de Vic – SICHV*).

To collect in a systematic and organized way all the clinical items necessary for the study, a special Google Form was created (see **Annex 3**). It allowed to gather all the data directly in a spreadsheet. The privacy and safety of the form was assured.

Among the strategies to increase the quality of the data, the collection has been carried out by a single person (by the main researcher), thereby enabling to follow the same criteria for all patients. With the aim of guaranteeing patients' confidentiality, the person in charge of collecting all the data has signed a contract which allows the access and processing of the personal data of the patients (see *chapter 8. Ethical considerations*).

Once the data collection was concluded, the spreadsheet automatically created by the Google form was easily moved to SPSS program.

- STUDY VARIABLES

Variables collected in the study's sample (88 patients) are:

- Demographic data:
  - Age: expressed in years. The age considered for the study was the one presented by the patient at the time of the first visit at the RDU.
  - Gender: woman or man.
- Assistance features:
  - Origin of referral: primary health care, emergency department, outpatient care facilities or hospital inpatient care.
  - Number of visits needed at the RDU until the final diagnosis was achieved.
  - In-hospital admission need throughout the follow-up.
  - Timing: calculated in calendar days.
    - Days since the referral until the first appointment at RDU.
    - Days since the first appointment at RDU until the final diagnosis is achieved.

        - Days since the diagnostic test (radiology test, endoscopic techniques…) was requested until the corresponding test report.
        - Days since the medical report was available until the next visit at the RDU.

- Data collected during the first visit at RDU:
    - Toxic habits:
        - Smoking: smokers, ex-smokers and non-smokers. Patients were considered ex-smokers if their consumption was more than 10 pack-years, and non-smokers if they have never smoked or their consumption was less than 10 pack-years.
        - Alcohol consumption: presence or absence of risky consumption alcohol. Patients were considered to present risky alcohol consumption if their average alcohol consumption ranged from 20 to 40g per day for women and from 40 to 60g per day for men (31).
    - History of functional pathology: presence or absence of functional pathology in patients' medical records.
    - Physical examination:
        - Clinical impression: organic or functional. In patients' medical history, clinicians noted what their first impression was about patients' CS according to their clinical eye: if CS was due to an organic disease or functional disease.
        - Weight loss: expressed in kg/month.
    - Laboratory data of the blood analysis realized at the first visit at the RDU:
        - Hemogram: haemoglobin, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), white blood cell count, platelet count.
        - Coagulation panel: international normalized ratio (INR).
        - Liver function tests: albumin, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), gamma glutamyl transpeptidase (GGT), alkaline phosphatase, total bilirubin and lactate dehydrogenase.
        - Lipid panel: total cholesterol.
        - Renal panel: glomerular filtrate.
        - Acute-phase reactants: C-reactive protein and erythrocyte sedimentation rate (ESR).
    - Data of urinalysis realized at the first visit at the RDU: pathological (urinalysis abnormalities as haematuria, leukocyturia, proteinuria or casts), non-pathological (absence of urinalysis abnormalities) or test not performed.
    - Data of chest radiographies realized at the first visit at the RDU: pathological (congruent with CS), non-pathological (absence of pathology or incongruent with CS) or test not performed.

  - Data of abdominal echographies realized throughout the follow-up at the RDU: pathological (congruent with CS), non-pathological (absence of pathology or incongruent with CS) or test not performed.

- Complementary studies realized throughout the follow-up:
  - Number of complementary studies realized by patient.
  - What complementary studies were realized by patient.
  - Complementary studies significance:
    - To determine whether any of the tests realized was the key to the diagnosis.
    - Among the tests performed, which one was the key to the diagnosis.
    - Main reason why the test was the key to the diagnosis: by confirming what organic pathology caused the CS or by ruling out organic pathology that might cause CS.
- Diagnostic entities of CS: entity that caused CS to the patient. If patient was diagnosed with cancer, presence or absence of metastasis at the time of the diagnosis was also collected.

  All the causes of CS have been divided into 4 main categories: **1)** neoplastic; **2)** organic/non-neoplastic; **3)** functional and **4)** non-organic/non-functional (unknown aetiology).

  In **neoplastic diseases group**, all cancers were included. In **organic/non-neoplastic diseases group**, all non-functional (understanding psychiatric diseases as functional diseases) and non-neoplastic (understanding cancers as neoplastic diseases) were included (digestive diseases, infections, rheumatic diseases, diseases caused by drugs or toxics, etc.). In **functional diseases group**, all psychiatric disorders were included. And finally, in **non-organic/non-functional diseases group**, patients with CS of unknown origin after ruling out neoplastic, organic and functional causes were included.
- Mortality in cancer context:
  - If patients diagnosed with cancer were still alive or not at the moment of the data collection.
  - Time passed (in days) since the cancer diagnosis until death in patients with cancer.

Once all data were collected and the database was created, it has been submitted to a dissociation process, so patients' identity remain dissociated from personal data. Thus, patients' confidentiality has been constantly respected.

Data have been revised before statistical analysis was done, in search of unusual or illogical values and transcription or coding error.

Extra data have been collected and their analysis will not be done to achieve the objectives of this project. These will be analysed in a future according to researchers' interest.

- STATISTICAL ANALYSIS

All statistical analyses were performed using the software Statistical Package for the Social Sciences (SPSS v.15.0) for Windows (32).

- **Univariate descriptive analysis**

For the univariate analysis, variables have been defined as qualitative or quantitative variables.

→ Variables considered as qualitative (categorical): gender, origin of referral, toxic habits (smoking and alcoholism), history of functional pathology, clinical impression, general appearance, results of basic tests (urinalysis, chest radiography and abdominal echography), complementary studies, complementary studies significance and the final cause of CS.

→ Variables considered as quantitative: age, number of visits at the RDU, timings at the RDU, laboratory data of blood analysis, number of complementary studies by patient, survival time in patients with cancer.

Measures of central tendency (mean, median) and dispersion (standard deviation [SD], interquartile range [IQR]) have been calculated for quantitative variables. Qualitative (categorical) variables have been expressed in frequencies and percentage.

Graphical representations of data have been used to ease a visual analysis. For qualitative data or discrete (quantitative) data, bar graphs and pie graphs have been portrayed. For continuous (quantitative) data, histograms and frequency polygons have been used. Boxplots have been used to allow a graphical display of the distribution of asymmetric data.

As mentioned above, due to the small sample size, we opted to perform a descriptive analysis as a first step. In a future, extended bivariate analysis and multivariate analysis will be considered. However, the development process of the bivariate and multivariate analysis is described below.

- **Bivariate analysis**

Generally, continuous variables in our study did not present a normal distribution. Therefore, non-parametric will need to be used for statistical hypothesis testing.

Comparisons between continuous variables will be performed by Student t-test when data have a normal distribution. When continuous variables do not present a normal distribution, the Mann-Whitney-U test or Kruskal-Wallis test (both non-parametric test) will be used.

Comparisons between categorical data will be done by χ^2-test.

For all tests, a $p<0.05$ will be considered statistically significant.

- **Multivariate analysis**

For the multivariate analysis, generalized lineal models with binomial link function (equivalent to logistic regression), Gaussian link (equivalent to lineal regression) and Poisson link (equivalent to Poisson regression) will be specified for dichotomous, continuous and discrete data, respectively. As explanatory variables, all the variables explained above will be introduced. The purpose of this analysis is to build a risk equation to determine the probability of cancer diagnosis (generally and according to the localization) at the time of the first visit at the RDU (depending on the variables).

8. ETHICAL CONSIDERATION

The current study has been performed respecting all the ethical principles and human rights regarding medical research, expressed in the policy statement "Declaration of Helsinki (DoH) of Ethical Principles for Medical Research Involving Human Subjects"(33), signed by the World Medical Association (WMA), in June 1964. The last version of this policy statement (conducted in October 2013) is the official one at the present time (33).

Regarding the articles 22 and 23 of the DoH (34), a research protocol (see **Annex 4**) was presented to the concerned research ethics committee (REC) ("Comitè Ètic d'Investigació Clínica de la Fundació d'Osona per a la Recerca I l'Educació Sanitària (FORES)). The study was approved on 31st of October 2017 and the study began afterwards (see **Annex 5**).

Patients' personal data have been strictly confidential, according to the "Ley orgánica 15/1999, de 13 de diciembre, de Protección de Datos de Carácter Personal" (35) and the "Ley orgánica 41/2002, de 14 de noviembre, básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica" (36).

Moreover, the person in charge (main researcher) of collecting all the data has signed a contract which allows the access and processing of the personal data of the patients (see **Annex 6**). All data regarding to patients' identity were dissociated from personal data, and thus, respecting patient's right to confidentiality. Only the main researcher and the FDP tutor had access to the database and they assure that personal data of the patients will not be distributed at any time.

The investigators of this study declare no conflict of interest.

9. RESULTS

1. CHARACTERISTICS OF THE PATIENTS

From May 1st 2015 to April 31st 2017, 93 patients were visited at the RDU of constitutional syndrome of HUV, of whom 5 were carefully excluded of the study (none of them presented any CS clinical features in the clinical interview). Among the 88 included patients, the mean age was 72,3 ± 14 years, with ages between 26 and 92 years, and 61,4% were men.

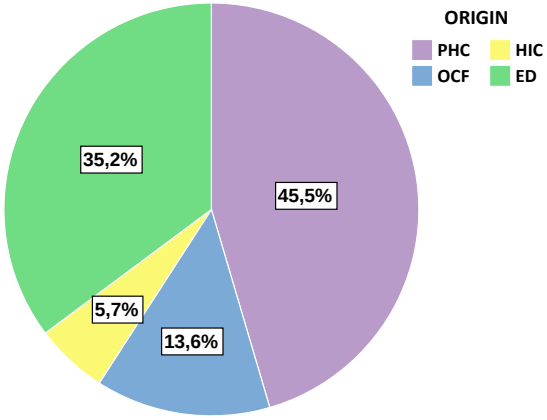


Figure 2. Origin of referral of patients with CS attended at the RDU. *PHC: Primary health care; OCF: Outpatient care facilities; HIC: hospital inpatient care; ED: emergency department.*

Patients referred from primary health care represented the largest group with 40 cases (45,5%) (**Figure 2**). and the remaining 48 patients were referred from emergency department (35,2%), from outpatient care facilities (13,6%) and from hospital inpatient care (5,7%).

The distribution by age, sex, smoking habit and alcohol habit of the 4 diagnostic groups is shown in **table 3**.

Table 3. Distribution by age, sex, smoking habit and alcohol habit of the 4 diagnostic groups

		Neoplasia	Organic/non-neoplastic disease	Functional disease	Non-organic/Non-functional disease
	n (%)	33 (37,5)	27 (30,7)	20 (22,7)	8 (9,1)
Age	*years ± SD*	74,61 (10,35)	67,1 (18,2)	74,9 (8,5)	74,4 (18,9)
Sex	*W (%) / M (%)*	9 (27,3) / 24 (72,7)	10 (37) /17 (63)	11 (55) / 9 (45)	4 (50) / 4 (50)
Smoking	*Smokers (%) / ex-smokers (%) / non-smokers (%)*	6 (18,2) / 11 (33,3) / 16 (48,5)	3 (11,1) / 5 (18,5) / 19 (70,4)	1 (5) / 4 (20) / 15 (75)	0 (0) / 2 (25) / 6 (75)
Risky alcohol consumption	*Yes (%) / No (%)*	4(12,1) / 29 (87,9)	1(3,8) / 26 (96,3)	1(5) / 19 (95)	1(12,5) / 7 (87,5)

W: women; M: men; SD: standard deviation.

The largest diagnostic group was neoplasia, including 33 patients (37,5%). Neoplasia group was followed by organic/non-neoplastic disease group (30,7%), functional disease (22,7%) and non-organic/non-functional disease (9,1%). The youngest age group, with an average of 67,1 years, was the group of organic/non-neoplastic diseases. Men were more frequent than women in all diagnostic groups, except in the group of functional diseases and the group of non-organic/non-functional diseases. In the group of functional diseases, women (55%) were more frequent than men (45%); and in the group of non-organic/non-functional disease, there was an equal number of women and men (4 cases for each). With reference to

toxic habits, most of the patients were non-smokers in all the diagnostic groups, except in the group of neoplasia (48,5%), in which 51,5% of the patients were smokers and ex-smokers. Most of the patients did not present a risky alcohol consumption in any of the diagnostic group.

2. RDU EVALUATION

2.1 GENERAL EVALUATION

Table 4. Assistance activity according to different procedures

Referral – RDU (days)		RDU – Diagnosis (days)		Test request – medical report (days)		Medical report – Next visit (days)		Nº of visits (N)	
Mean	*Median*	*Mean*	*Median*	*Mean*	*Median*	*Mean*	*Median*	*Mean*	*Median*
4 (3,2)	3 [2 – 5,5]	11,4 (20,1)	3 [0 – 15,5]	11,3 (15,1)	5,5 [0 – 16]	8,1 (15,4)	3,5 [0 – 9,5]	1,8 (0,8)	2 [1 – 2]

Statistical dispersion of mean is expressed with standard deviation (SD). Statistical dispersion of median is expressed in interquartile range [Q1 – Q3].

Table 4 shows the summary statistics (central tendency and statistical dispersion) of the days taken by the RDU according to different procedures (all of them are expressed in calendar days): 1) Referral – RDU: time in days taken from the referral until the first visit to the RDU; 2) RDU – Diagnosis: time in days from the first visit at the RDU until the diagnosis; 3) Test request – medical report: time in days from the diagnostic tests requests until the medical report; 4) Medical report – next visit: from the medical report until the next visit and 5) Nº of visits: number of visits needed at the RDU.

The RDU of HUV took a median of 3 days (IQR: 2 to 5,5 days) to visit for the first time patients with CS since they were referred. The median time since the first visit at the RDU until the diagnosis was 3 days (IQR: 0 to 15,5 days). Patients needed a median of 2 visits (IQR: 1 to 2 visits) at the RDU.

During the patient's follow-up (since the first visit at the RDU until the medical discharge), 13 (14,8%) patients needed to be hospitalized due to CS-related symptoms (6 of whom at the first appointment at the RDU).

Complementary diagnostic tests were performed in 69 patients. After performing these diagnostic tests and getting the medical report, there were different situations that can arise:

1. The patient was revisited by the RDU: it occurred in 60,9% of all the cases. The mean and median time (in days) between the medical report and the next visit at the RDU is exposed in **table 4**.

   Pathologies that were more frequently revisited were malignant neoplasms (18 cases, 42,9% of revisited patients) and organic/non-neoplastic diseases (13 cases, 31% of revisited patients).

2. The patient was straight referred to the indicated specialist (as oncologists or psychiatrists): it occurred in 17 cases (24,6% of the cases). Pathologies that were more frequently directly referred

were malignant neoplasms (7 cases) and psychiatric disorders (4 cases).

3. The patient did not come back to the RDU: it occurred in 5 cases (*these patients are examined more closely further in this section*).

4. The patient had to be hospitalized: in these patients (5 cases), the diagnostic process was performed directly during the hospitalisation. Once the patients were discharged from hospital, the RDU was available for new visits if needed.

Diagnostic tests were not performed in 19 patients. These patients were followed-up by the RDU until they could be discharged (8 patients) or until they were straight referred to the indicated specialist (5 cases). In the case of 5 patients, they did not come back to be revisited at the RDU (*as before, these patients are examined more closely further in this section*). The remaining case needed to be hospitalized.

The reasons why some patients did not come back were reviewed. Concerning the functioning of the RDU, the patients were responsible to inform that the requested tests were already done in order to schedule the next visit. The reasons detected were: 1 patient was referred to the outpatient care facility of internal medicine service; 2 patients were referred back to PHC (the first one to have the PHC check the test report, and the second one to be closely followed throughout his palliative care); 2 patients' follow-up was lost (the first one because of an important language barrier, and the second one did not come to the scheduled visit by choice). The remaining 5 patients did never come back for no apparent reason. However, in these patients, the tests were not pathological.

Table 5 shows the summary statistics according to the origin of the referrals. The RDU took a median of 3 days to visit patients referred from PHC, ED and OCF. These patients were visited a median of 2 times (IQR: 1 to 2). Meanwhile, patients referred from HIC were visited after a median of 5 days (IQR: 4 to 6) and they needed a median of 1 visit (IQR: 1 to 2).

Table 5. Summary statistics according to the origin of referrals

	Referral – RDU (days)		Nº of visits (N)	
	Mean	*Median*	*Mean*	*Median*
PHC	3,4 (2,3)	3 [1 – 5]	1,8 (0,9)	2 [1 – 2]
ED	4,7 (4,4)	3 [2 – 6,5]	1,7 (0,7)	2 [1 – 2]
OCF	3,7 (1,8)	3 [2,5 – 5]	1,8 (0,9)	2 [1 – 2]
HIC	6,2 (3,3)	5 [4 – 6]	1,6 (0,9)	1 [1 – 2]

Statistical dispersion of mean is expressed with standard deviation (SD). Statistical dispersion of median is expressed in interquartile range [Q1 – Q3].

Table 6 shows the summary statistics according to the 4 main diagnostic groups.

In the case of patients diagnosed with neoplasia, the RDU visited them a median of 2 days (IQR: 2 to 4) after the referral. It took a median of 5 days (IQR: 0 to 17) to reach the diagnosis of cancer. Once the

diagnostic test was performed and the test report obtained, patients with neoplasia were revisited a median of 1 day (IQR: 0 to 3,5) later.

For patients with functional disease, the median time to achieve the diagnosis was 0 days (IQR: 0 to 4). For these patients, the median time until the diagnostic test was performed and the test report obtained was 12 days (IQR: 2 to 23). They were revisited 8 days (IQR: 7 to 15) later.

Table 6. Assistance activity according to the 4 main diagnostic groups

	Referral – RDU (days)		RDU – Diagnosis (days)		Test request – medical report (days)		Medical report – next visit (days)		Nº of visits (N)	
	Mean	*Median*	*Mean*	*Median*	*Mean*	*Median*	*Mean*	*Median*	*Mean*	*Median*
Neoplasia	3,4 (3,8)	2 [2 – 4]	12 (18,4)	5 [0 – 17]	9,1 (11,9)	4,5 [0 – 14,5]	2,3 (3)	1 [0 – 3,5]	1,7 (0,8)	2 [1 – 2]
Organic/non-neoplastic disease	4,7 (3,3)	5 [1,5 – 6]	13,3 (21,7)	5 [0 – 19]	10,5 (14,2)	3,5 [0 – 17,5]	14,3 (25)	8 [0 – 15]	1,9 (1)	2 [1 – 2]
Functional disease	4,6 (2,5)	4 [3 – 6,5]	8,3 (22)	0 [0 – 4]	18,8 (23,4)	12 [2 – 23]	11,7 (8,6)	8 [7 – 15]	1,9 (0,7)	2 [1 – 2]
Non-organic/Non-functional disease	3 (1,5)	3 [2 – 3,5]	7 (9,9)	7 [0 – 14]	9,4 (7,9)	8,5 [3 – 15,5]	3,5 (5)	3,5 [0 – 7]	1,1 (0,4)	1 [1 – 1]

Statistical dispersion of mean is expressed with standard deviation (SD). Statistical dispersion of median is expressed in interquartile range [Q1 – Q3].

More specific summary statistics are exposed in **Annex 7**: the assistance activity according to the final diagnoses is reflected in **table 7** and the assistance activity according to cancer types is reflected in **table 8**.

2.2 DIAGNOSTIC TESTS EVALUATION

2.2.1. BASIC TESTS

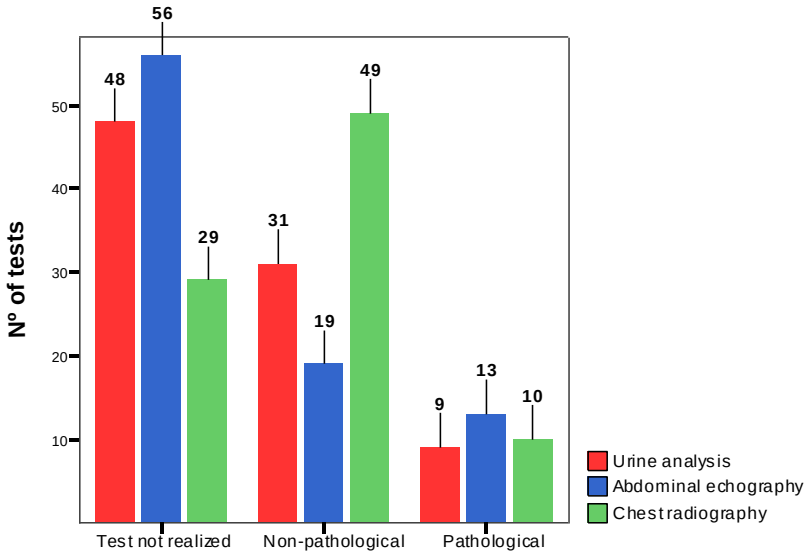


Figure 3. Performance and results of basic tests realized at the first visit

As basic tests possibly performed on the first visit, there are blood analysis, urine analysis, chest radiographies and abdominal echography (**Figure 3**). A blood analysis was performed in all patients during their first appointment.

Chest radiographies were performed in 59 patients (67,1%), 10 (11,4%) of which were pathologic (consistent

with CS).

Abdominal echography was performed in 32 patients (36,4%), and 13 of which were pathologic (consistent with CS).

2.2.2. COMPLEMENTARY TESTS

The number of tests per patient is detailed in **table 9**. If no test was performed, it could be for two reasons: no specific further studies were required to get the diagnosis, or the indicated studies were already ordered by other clinicians at the time of the first visit at the RDU.

Table 9. Number of tests per patient

Nº of tests per patient	N (%)
0	19 (21,6)
1	29 (33)
2	24 (27,3)
3	13 (14,8)
4	3 (3,4)

The total number of complementary tests performed are shown in **table 10** (see **Annex 7**). Abdominal CTs were the most requested complementary study, followed by endoscopic techniques (gastroscopy and colonoscopy).

In 57 patients (64,8%), diagnostic tests were the key to get the final diagnosis. The most helpful tests were computed tomographies (especially abdominal CT), abdominal echographies and gastroscopies.

These tests were the key to the diagnosis by confirming organic pathology in 40 patients and by ruling it out in 17 patients (especially in psychiatric disorders).

3. DIAGNOSTIC ENTITIES OF CS

In **table 11**, the diagnoses assigned as the responsible for the CS are shown (the 4 main diagnostic groups are also reflected). A diagnosis that could explain the CS was reached in 90,1 % of the patients. The most frequent cause of CS was cancer: neoplasms were diagnosed in 33 patients (37,5%). Cancer diagnosis was followed by psychiatric diseases (22,7%) and digestive diseases (13,6%).

Malignant causes are discussed in chapter *3.1. Neoplasia*.

In psychiatric diseases, disorders related to depression and anxiety were the most frequent causes. One of them was diagnosed with a depressive episode in the context of a bipolar disorder.

Regarding the organic but non-neoplastic diseases, the diseases of digestive system represented the third most common cause of CS. Among all the digestive disorders diagnosed, oesophageal motility disorder, choledocholithiasis and undefined digestive disorder were the most frequent. In patients with the final diagnosis of undefined digestive disorder, a complete study was done because of the comorbidities they presented. In both cases, a neoplastic cause was ruled out and the CS cause was self-limited.

In 8 patients, any disease was found to explain the CS. No justifiable cause was found in 5 of them after a complete evaluation, and they were discharged from the RDU with option to reconsultation at any time. One of the five patient was admitted to the hospital one month later because of a COPD (*Chronic Obstructive Pulmonary Disease*) decompensation due to an infection. In the other 3 cases, follow-up by the RDU was lost before the study was concluded: in 1 case, the patient did never come back to the corresponding appointment and in the other 2 cases, adequate follow-up was not possible due to a significant language barrier in one of them and a mental disability problem in the other. At the time of the data collection, in these 3 last patients, any alternative diagnosis was detected to justify the CS after the visit at the RDU.

Table 11. Causes of CS in 88 patients

Causes of constitutional syndrome	N (%)	n	%
NEOPLASIA			
Cancer	33 (37,5)		
Pancreatic		7	8
Colon		5	5,7
Gastric		4	4,5
Lymphoma		3	3,4
M1 without primary tumour		3	3,4
Prostatic		3	3,4
Lung		3	3,4
Other cancers[1]		*5*	*5,5*
FUNCTIONAL DISEASE			
Psychiatric diseases	20 (22,7)		
Depression – Anxiety		19	21,6
Bipolar disorder (depressive episode)		1	1,1
ORGANIC / NON-NEOPLASTIC DISEASE			
Digestive diseases	12 (13,6)		
Oesophageal motility disorder		2	2,2
Choledocholithiasis		2	2,2
Other digestive diseases[2]		*6*	*6,6*
Undefined digestive disorder		2	2,2
Rheumatic disease	6 (6,8)		
Polymyalgia rheumatica		2	2,3
Sarcoidosis		2	2,3
Giant cell arteritis		1	1,1
Undefined rheumatic disease		1	1,1
Infectious disease	3 (3,4)		
Bronchiectasis infection		2	2,3
Tuberculosis		1	1,1
Drugs - toxics	2 (2,3)		
Digoxin		1	1,1
Ethanol		1	1,1
Miscellaneous	4 (4,4)		
Radicular pain		1	1,1
Advanced heart failure		1	1,1
Abdominal aortic aneurysm		1	1,1
Obstructive uropathy		1	1,1
NON-ORGANIC/NON-FUNCTIONAL DISEASE			
CS of unknown aetiology	8 (9,1)		

1. *Other cancers*: breast cancer, retroperitoneal neoplasia, ovarian cancer, vesical cancer and digestive neoplasia **(1 case for each).**
2. *Other digestive diseases*: chronic diarrhoea, Barrett oesophagus, gastritis, lactose intolerance, digestive intolerance, intussusception **(1 case for each).**

Overall, history of functional pathology was observed in 23 patients (26,1%). Of these patients, 56,5% ended with a functional diagnosis and only 8,7% with a cancer diagnosis. Conversely, 47,7% of patients without history of functional pathology had a cancer diagnosis, followed by organic diseases in 30,8% of the patients. So, previous psychiatric disease was associated with non-organic causes of CS ($p < 0,001$).

Regarding clinician's clinical impression about the patient, clinicians considered that a functional disease may be the cause of CS in 22 patients (25% of

all patients) and an organic disease (in this case, including neoplastic diseases) in the remaining cases. When the clinical impression was organic, it was associated with a final organic entity as the cause of CS ($p < 0,001$). The sensitivity and the specificity of an organic clinical impression was 96,7% and 80%, respectively.

On average, patients lost 3,01 ± 1,6 kg per month of weight (no statistical significance was detected). In 30,7% of all patients, weight loss was not quantified in the medical records, but specified.

3.1 NEOPLASIA

Among the malignant neoplasms (33 cases), the most frequent ones were the digestive neoplasms: pancreatic cancer was found in 7 patients (21,2% of all cancers), followed by colon cancer in 5 patients (15,2% of all cancers), and finally, gastric cancer in 4 patients (12,1% of all cancers).

The second group in frequency within malignant tumours were: lymphomas, prostatic cancer, lung cancer and metastasis without primary tumour. Each of them represented 9,1% of all cancers.

In some patients, the diagnostic process could not be completed: one patient had a retroperitoneal mass, but it was not possible to determine if it was a primary tumour or a metastasis; and in another patient, a neoplastic process was found (possibly a digestive tumour), but there was no time to complete the study because of the end-stage disease and the short time of survival.

In one of the patients, the diagnosis of gastric cancer was not done at the RDU at first, but a month later due to a hospitalisation. During the visit at the RDU, the decision of not performing any invasive test was made, taking in account the risk-benefit relation and the patient's fragility. The patient was closely followed up by the primary care physician until the hospitalisation.

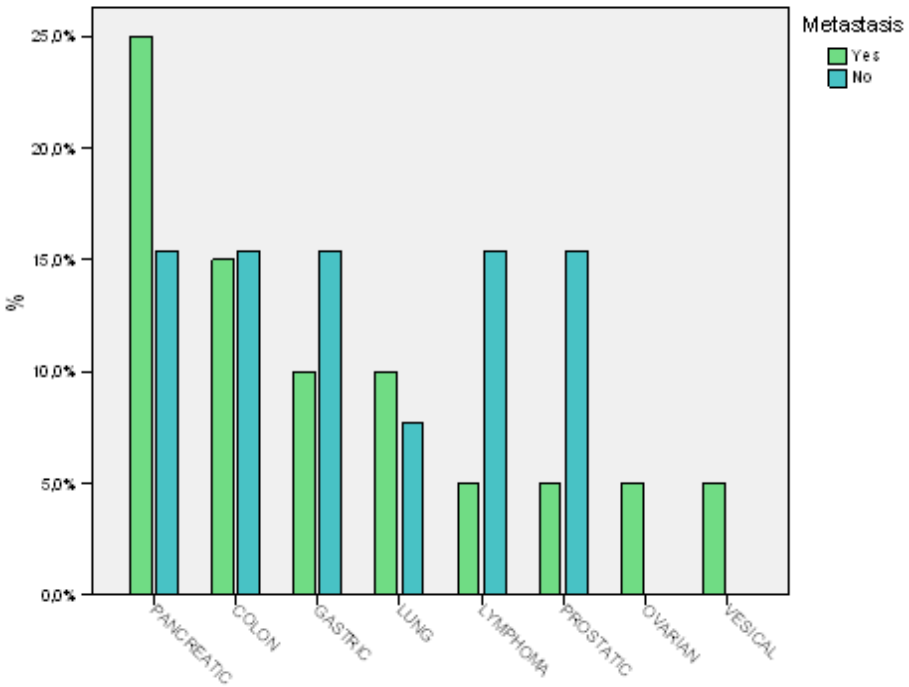


Figure 4. Metastasis according to types of cancer

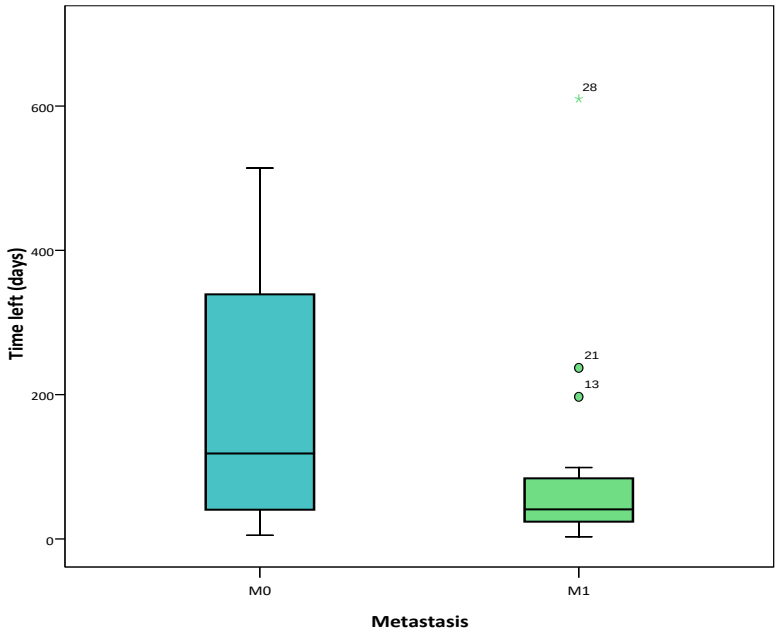
3.1.1 METASTASIS

60,6% of all the patients diagnosed with cancer (20 patients) presented metastasis (M1) at the moment they were visited at the RDU and the cancer was diagnosed. Pancreatic cancer was the tumour which presented more frequently metastasis (71,4% of pancreatic cancer), followed by colon cancer (60% of colon cancer), and gastric and lung

cancer (50%). **Figure 4** shows the percentage of metastasis according to the most diagnosed cancers ("metastasis without primary tumour" has not been included).

3.1.2 MORTALITY

Among patients with cancer diagnosis, 25 of them have died (75,8%). Overall, once patients got their cancer diagnosis, the mean time left until death was 126 ± 164 days. The median time left was 48 [27 – 140] days. The mean time left of patients with metastasis (M1) at the time of diagnosis was 96 ± 147 days (median time left of 41 [24 – 84] days). In patients with no metastasis (M0), the mean time left was 189 ± 190 days (median time left of 118,5 [40,5 – 339] days). Therefore, the survival time of patients presenting a metastasis (or disseminated cancer) was 34,6% of the survival time of those without metastasis (or localized cancer).



M0 = no metastasis at the time of cancer diagnosis; M1 = metastasis at the time of cancer diagnosis

Figure 5. Distribution of survival time depending on metastasis

The distribution of survival time depending on the presence or absence of metastasis is shown in **Figure 5**.

Table 12 (*on the following page*) shows the number of patients who are alive or dead according the presence for each type of cancer. The survival time of patients who died is also exposed. Patients diagnosed with metastasis without primary tumour had the worst prognosis, with a median of survival time of 19 [11 – 59] days, followed by patients with digestive tumours (especially colon cancer with metastasis). Patients with the best prognosis were the ones diagnosed with lymphoma without extranodal involvement.

Table 12. Survival according to cancer types and metastasis

		ALIVE	DEAD	Survival time	
				Mean	***Median***
Pancreatic					
	M0	0	2	51 (65,1)	51 [5 – 97]
	M1	0	5	87 (87,8)	59 [43 – 84]
Colon					
	M0	2	0	-	-
	M1	1	2	31,5 (13,4)	31,5 [22 – 41]
Gastric					
	M0	1	1	-	-
	M1	1	1	-	-
Lymphoma					
	M0	0	2	278,5 (195,9)	278,5 [140 – 417]
	M1	0	1	-	-
M1 without primary tumour					
	M0	-	-	-	-
	M1	0	3	40,33 (51,4)	19 [11 – 59]
Lung					
	M0	0	1	-	-
	M1	0	2	61 (32,5)	61 [38 – 84]

10. DISCUSSION

Constitutional syndrome is a set of symptoms that can be the first manifestation of a wide range of diseases. When clinicians face a patient presenting a CS, their objective is to detect the underlying cause. Sometimes, this task becomes a challenge because of the varying presentation and aetiologies that CS can present. Amongst the most frequent aetiologies described in the medical literature, cancer is easily one of them. It may not always be the most frequent cause according to the study, but it has an important incidence in any of it.

When tumours are the cause of CS, it is more common to be a malignant tumour than a benign one. Furthermore, when a malignant tumour presents itself with CS, it has often a bad prognosis (15).

RDUs represent an alternative to standard care. With their creation, patients with potentially serious diseases could benefit from an accelerated and facilitated diagnostic process. Consequently, RDU's objectives are to reduce diagnostic delays, improve coordination with PHC and other health services, and prevent unnecessary admissions. Thus, in one hand, it will provide an increase in the quality of healthcare and patients' satisfaction and comfort. And on the other hand, hospitals may optimize their resources.

The RDU of HUV takes a median of 3 days to visit patients with CS since they are referred and 3 more days to achieve the diagnosis. In the context of potentially serious diseases, as cancer, the RDU takes a median of 5 days to diagnose them, in a range of 0 to 17 days. Once complementary tests and medical reports were ready, patients diagnosed with cancer were revisited in a median of 1 day, so the best therapeutic approach could be decided.

RDU GENERAL EVALUATION

Overall, the RDU of HUV took a median of 3 days to visit patients with CS from when they were referred. Depending on the origin of referrals, this time varied. While it took the same time for patients from PHC, ED and OCF, patients from HIC took a little longer. This situation may be because the responsible clinicians of the referral recommended the appointment at the RDU by the time the test reports were ready, or because they wanted to schedule a follow-up visit to complete the study.

Depending on the diagnostic group, the time taken until patients were seen for the first visit by a clinician varied. Clinicians do not normally prioritise the visit because they do not know the diagnostic orientation. Even though, patients within the group of neoplasia were visited in 2 days. This may be because the responsible clinicians of the referral emphasise the need of visit the patient as fast as possible.

Generally, regarding the time of the diagnostic process, it took a median of 3 days to get the final diagnosis. More precisely, it took longer among the diagnostic groups (neoplasia, organic / non – neoplastic diseases and non – organic / non – functional disease) which complementary tests are normally required to get the

diagnosis. Conversely, functional diseases were rapidly diagnosed because of their clinical presentation during the visit. In some of these patients, the clinician may find appropriate to request complementary test to rule out organic diseases even if the functional diagnostic is considerably clear. In the latter case, the time between the test request and the medical report may take longer due to a low suspicion of an organic cause, and thus tests are not requested with a high priority.

In HUV, the priority in diagnostic test performing depends not only on the clinicians of the RDU, but also on the radiologists' judgement. This may be a limiting factor to the agility of the diagnostic process at the RDU. Radiologists constantly receive requests for radiological tests from other specialities. In other specific rapid diagnostic circuits, such as lung cancer RDC, defined periods of time are established so radiological tests can be performed whenever it is needed. This may be an improvement solution for the RDU. However, most of the tests requested with priority due to a high suspicion of organicity and neoplastic pathology were performed fast enough. In our study, we can verify that the priority in diagnostic tests has been effective in terms of potentially serious diseases.

The RDU only took 1 day to revisit patients with a cancer diagnosis after the complementary test, so the best therapeutic approach to these patients may be conducted in the most effective and appropriate way. The agility of revisiting the patients has not changed even if they have been diagnosed with a cancer in the terminal stage and curative treatments are no longer possible. In this way, it lets these patients and their families receive the most adequate palliative and supportive care in an appropriate way. In addition, the RDU has the capacity to coordinate different medical disciplines and thus to work closely for the best of the patient.

Once neoplastic processes were ruled out among patients with a functional, organic/non-neoplastic and non-organic/non-functional disease, the clinicians of the RDU did not revisit these patients so immediately as patients with cancer. In the case of organic/non-neoplastic diseases, and more precisely in digestive disorders, clinicians may have the medical report of the endoscopic techniques but not the medical report of the biopsies.

Amongst all the patients, 10 of them did not come back to the RDU for the follow-up or to be discharged. On the one hand, in the case of 3 patients, it occurred intentionally: 2 were referred to PHC (the first one to have the primary health physician check the test report, and the second one to be closely followed throughout his palliative care); and the latter case, the control visit was performed at the outpatient care facility of internal medicine (the responsible doctor was a medical resident who had visited the patient for the first time at the RDU). Both alternative ways are considered as valid to conclude these patients' follow-up, as it preserves a fast and agile follow-up. Furthermore, if needed, these patients could be referred again to the RDU.

But, on the other hand, 7 patients did not come back to the RDU, even though it was not the RDU's intention. In 2 patients, there was a loss of their follow-up because of an important language barrier in one case and the patient's willing choice in the other case. But in 5 patients, there was no apparent reason (even if all of them had no pathological test). The most likely reason was the improvement of their CS and its spontaneous remission. However, it is not possible to know it for certain. Nevertheless, the detection of these cases is certainly concerning, as it means that the RDU may have a follow-up hole in 6% of their patients, which is not a minor percentage.

Because of the pressure on the unit and the medical team (clinicians and nurses), it is not feasible to monitor all the requested tests (its performing and evaluation) of all RDU's patients (generally, RDU includes patients with anaemia, lymphadenopathies, fever…). For this reason, the decision of making the patients responsible to notify the RDU (once the tests had been carried out) was made. Subsequently, the clinician in charge checked the test reports and decides what stance to take. This approach may be significantly improvable if an administrator was available (even if this person worked part-time). This way, patients' approach may be speed up and organized. In fact, the increase in personnel in the RDU team has been already claimed, but for the moment it has not been approved. Hence, there is the need to find a solution to this point of improvement.

In the recent years, many RDUs have emerged in IMS and some of them have already evaluated their functioning in terms of agility and speed. The time taken from the referral until patients were visited for the first time at the RDU varies from 1,4 days in the RDU of "Complejo Hospitalario de Palencia" (28) to 4,5 days in "Hospital General de Granollers" (HGG) (14). Normally, RDUs took less than 5 days to attend patients for the first time (14,28,37,38). Considering the time since the first visit until the diagnosis, it varies from 5,7 days in the RDU of HGG to 15 days in "Hospital Mateu Orfila"(38). The other RDUs used to take 8 to 9 days to get the diagnosis (28,37,39).

All these studies evaluated their functioning including all reasons for consultation (anaemia, febrile syndrome, lymphadenopathies…) and did not focus on CS. It was one of the most frequent reasons of referral and its frequency varied from 13% (37) to 21% (40). Our results cannot be compared to these previous evaluations, due to the differences in the study populations. However, it gives us an idea of the maximum time of delay that a RDU may have.

DIAGNOSTIC TEST EVALUATION

With reference to basic tests, blood analysis is always performed at the first appointment at the RDU. Analytical parameters have been collected in order to be analysed in a near future according to the researchers' objectives. The main objective is to find associations between them and the type of diagnosis.

Apart from blood analysis, urine analysis, chest radiographies and abdominal echographies were not regularly performed during the first visit. Clinicians decide what diagnostic test is the most appropriate depending on the diagnostic suspicion.

In the reviews of CS, abdominal echographies have been defined as a basic test. But, actually, it is not performed as a routine test. Moreover, this ultrasound technique needs of trained persons to be done, and thus it depends on their availability. In the case of our hospital, abdominal ultrasounds depend on the radiologists' availability and the pressure from the RDU to get the test performed, so the diagnostic process agility can be maintained.

For future clinical guidelines, abdominal echographies may be one of the first test to be considered in case of suspicion of organicity at an abdominal level, but it may not be included as a basic test.

Complementary tests were performed depending on the diagnostic suspicion, and 78,4% of all patients have performed at least 1 complementary test. Abdominal CTs were the most requested complementary study, and also the most useful and helpful test to confirm or rule out the final diagnosis.

At this point, any previous studies have evaluated what complementary test is the most useful in CS approach. Our results may help to carry out endorsed clinical guidelines, so CS approach could be unified among RDUs. It may also help to establish which complementary test achieved the highest diagnostic yield.

Unfortunately, our hospital does not have available PET/CT tests (*Positron Emission Tomography/Computed Tomography*), considered as one of the best screening test. If this test is needed, patients must be referred to another health care centre that covers a larger number of population. This makes the test less available. Furthermore, at the present time, PET-SCAN is reserved for situations which the diagnostic approach is more complex, and conventional test has been unable to get an accurate diagnosis.

DIAGNOSTIC ENTITIES OF CS

The most frequent causes of CS at the RDU of HUV were malignant neoplasms. Among malignant neoplasms, the most frequent ones were digestive tumours including pancreatic and colon cancers. Furthermore, in most patients diagnosed with cancer presented metastasis. Survival time could not be statistically associated to the presence of metastasis, but it was considerably less in patients with a diagnosis of disseminated cancer.

In the results of studies describing the cause of CS, cancer is constantly one of the most frequent causes, together with organic but non-neoplastic diseases. However, all these studies are difficult to be compared to each other because of their different methodology. First of all, the studied population normally came from hospitalized patients due to their CS (13,22,24,41,42). Just two research studies exposed the causes of SC in an area outside the hospital admission (23,43). Even then, one of these studies did not base its results

on a RDU, but on the outpatient care facilities of its hospital (23). And finally, some of the studies discussed just involuntary weight loss, but even if it is the main symptom of CS, they do not take into account patients with low weight loss but with the other accompanying CS features (asthenia and anorexia) (22–24).

Psychiatric disorders were the cause of CS in nearly a quarter of our sample, being the second most frequent diagnosis. Considering the average age of our sample, on the most part, our patients were mostly elderly. And, as suggested in previous studies, depression is one of the most frequent cause of anorexia and weight loss in patients older than 65 years old (13). This may reflect the higher probability of losing weight among elderly patients with depression than younger patients with this disorder.

Unlike other studies, where organic but non-neoplastic diseases were the second most frequent cause, it was the third cause in our sample. As pointed out above, this may due to higher probability of losing weight among elderly patients with depression.

Finally, with reference to patients whose final cause was not found (CS of unknown aetiology), none of them ended with potential serious diseases as cancer. Even if a complete evaluation was done and they were discharged from the RDU with option to reconsultation, most of them did not reconsult (except for 1 case, who was admitted one month later because of a COPD decompensation due to an infection). This may be because their symptoms were self-limited and the patient spontaneously improved.

To conclude, regarding to the CS approach and the final diagnosis of this entity, we want to emphasise the importance of an accurate anamnesis during the first visit to the RDU. A previous psychiatric disease is associated with non-organic causes, in the same way as an organic clinical impression is associated to organic causes. This may help to face better the approach of CS. Nevertheless, in the cases a patient presents history of functional pathology, this does not mean that a complete evaluation (with complementary test if needed) may not be done to rule out any organic aetiology. This is even more important regarding clinicians' clinical impression, which is a perception depending on a high degree of subjectivity and on the clinicians' professional experience.

11. LIMITATIONS

The first limitation of this study was due to its retrospective design. All the data were collected from the medical history of the patients, so sometimes the lack of information was possible. To minimise information bias, the data collection was realized in a systematic and organized way, so the required information and its quality was assured.

The review of patients' clinical evolution, with the purpose to detect alternative diagnoses onsets (specially in patients with non-neoplastic or non-organic diseases), was carried out through the medical information stored in the SICHV. As the only public hospital in the region of Osona, it makes it difficult for some diagnoses to get unnoticed. Nevertheless, it cannot be ruled out that a patient opted for private health care. Due to this assumption, the best follow-up may have been the combination of medical data from SICHV, PHC and from the patient (via telephone call).

Variables regarding timings of different procedures were collected and expressed in calendar days and not in working days (the RDU of HUV operates from Monday to Friday). Holiday periods of the RDU team and public holidays were not taken into account. And thus, there could be a limitation of the results of the RDU evaluation according to the different procedures. However, we evaluated an entity which sometimes can have a poor short-term prognosis (such as patients diagnosed with metastasis) so there is an important matter of time. For this reason, we considered appropriate to evaluate the timings in calendar days instead of working days.

Regarding to CS approach, there is a lack of endorsed practice guidelines which offers the best approach to these patients. In consequence, evaluating the appropriateness of clinicians' attitude could be difficult. At the time of the data collection, the different ways of proceeding between clinicians of the RDU supposed a further difficulty.

The reliance on other specialists, such as radiologist and endoscopists, for the prioritisation and the tests performing did not allow to make an exclusive self-criticism of the RDU.

Amongst the different working procedures of the clinicians at the RDU, there are elements of subjectivity that complicates their work systematization, its analysis and reaching valid conclusions.

- According to the clinical information provided by the clinician responsible of the referral, the visit at the RDU was more or less prioritised (even though it was always nimble).
- According to the information provided to the radiologist at the time of a test request, the tests performing were more or less prioritised.
- According to the test results (specially in those congruent with organicity or neoplastic pathology), the next visit at the RDU or the referral to the indicated specialist were more or less prioritised.

12. CONCLUSIONS

- ✓ The rapid diagnostic unit of constitutional syndrome of HUV has the ability to speeding up the diagnostic process of a patient with this clinical presentation. The RDU minimizes the waiting time for the first visit and also obtains the diagnosis of the underlying cause of CS in a short interval of time.

  In the case of potentially serious diseases, the unit is efficient in diagnosing patients with cancer. This is achieved through an effective coordination among clinicians from different specialities who need to be involved to get the diagnosis.

  As improvement points, the RDU must assure that 100% of these patients are closely followed up, and no loss of follow-up occurs in any case.

  Thus, we can conclude by saying that the RDU of HUV meets substantially all the general RDUs' main purposes: reduce diagnostic delays, establish a good coordination with PCH and the other health services, and prevent unnecessary admissions.

- ✓ The main underlying causes of CS from Osona region are similar to those presented in other studies, even if their respective methodologies are different. Malignant neoplasms are the most frequent cause of CS and psychiatric disorders are the most frequent non-organic cause. Psychiatric disorders constituted the second most frequent general cause.

- ✓ Patients with CS who ended up with a cancer diagnosis had a poor prognosis. More than 75% of them have died in less than two months. The prognosis was worse in patients presenting metastasis at the moment of the cancer diagnosis.

- ✓ The most used complementary test was the computed tomography. Abdominal CT, together with abdominal echographies and gastroscopies, were the most helpful tests to get the final diagnosis, both to confirm or rule out an organic cause.

- ✓ During the first visit, clinician's clinical impression of the organic nature of the cause of CS may be reliable. Nevertheless, an appropriate evaluation must be realized even if the clinical impression is functional.

13. WORK PLAN AND CHRONOGRAM SCHEME

This study has been conducted throughout a period of 4 months. It started on 12th September 2017 and ended on 15th January 2018.

It has been organized in the following phases:

1. **PHASE 1 – COORDINATION PHASE (1 month)**: *[main researcher and FDP tutor]*
   - **1.1. Meeting with the tutor:** the main researcher and the FDP tutor met for the purpose of discussing the research subject.
   - **1.2. Bibliographic research**: an extensive and rigorous research was realized by the main researcher about the current bibliographic information about SC and RDUs.
   - **1.3. Introduction and justification redaction**: written up by the main researcher.
   - **1.4. Establishment of the study**: during this phase, the study methodology (study design, study population, sample selection, inclusion/exclusion criteria, variables to collect, statistical analysis) has been decided by the main researcher and the FDP tutor.

2. **PHASE 2 – PROTOCOL WRITING (2 ½ weeks):** *[main researcher, FDP tutor and RCE]*
   - **2.1. Protocol composition:** a study protocol was written by the main researcher. This protocol was meant to be evaluated by the REC "Comitè Ètic d'Investigació Clínica de la Fundació d'Osona per a la Recerca I l'Educació Sanitària (FORES)". For this reason, it was written in Catalan language (see **Annex 4**).
   - **2.2. Protocol presentation to the RCE:** the study protocol was presented to the concerned RCE on 20th October 2017 in order to be evaluated and approved.
   - **2.3. Preparation of the data collection:** the Google Form used to collect all data was created by the main researcher, awaiting the protocol approval in the RCE.
   - **2.4. RCE approval:** the "Comitè Ètic d'Investigació Clínica de la Fundació d'Osona per a la Recerca I l'Educació Sanitària (FORES)" approved the study protocol on 31st October 2017.

3. **PHASE 3 – DATA COMPILATION (3 weeks):** *[main researcher and FDP tutor]*
   - **3.1. Data collection:** the data collection was performed by the main researcher. All the process was supervised by the FDP tutor.
   - **3.2. Data depuration:** the data depuration was jointly performed by the main researcher and the FDP tutor.

4. **PHASE 4 – STATISTICAL ANALYSIS OF COLLECTED DATA (3 ½ weeks):** *[main researcher]*
   - **4.1. Descriptive statistics:** it has been performed by the main researcher.
   - **4.2. Statistical inference:** it has been performed by the main researcher.

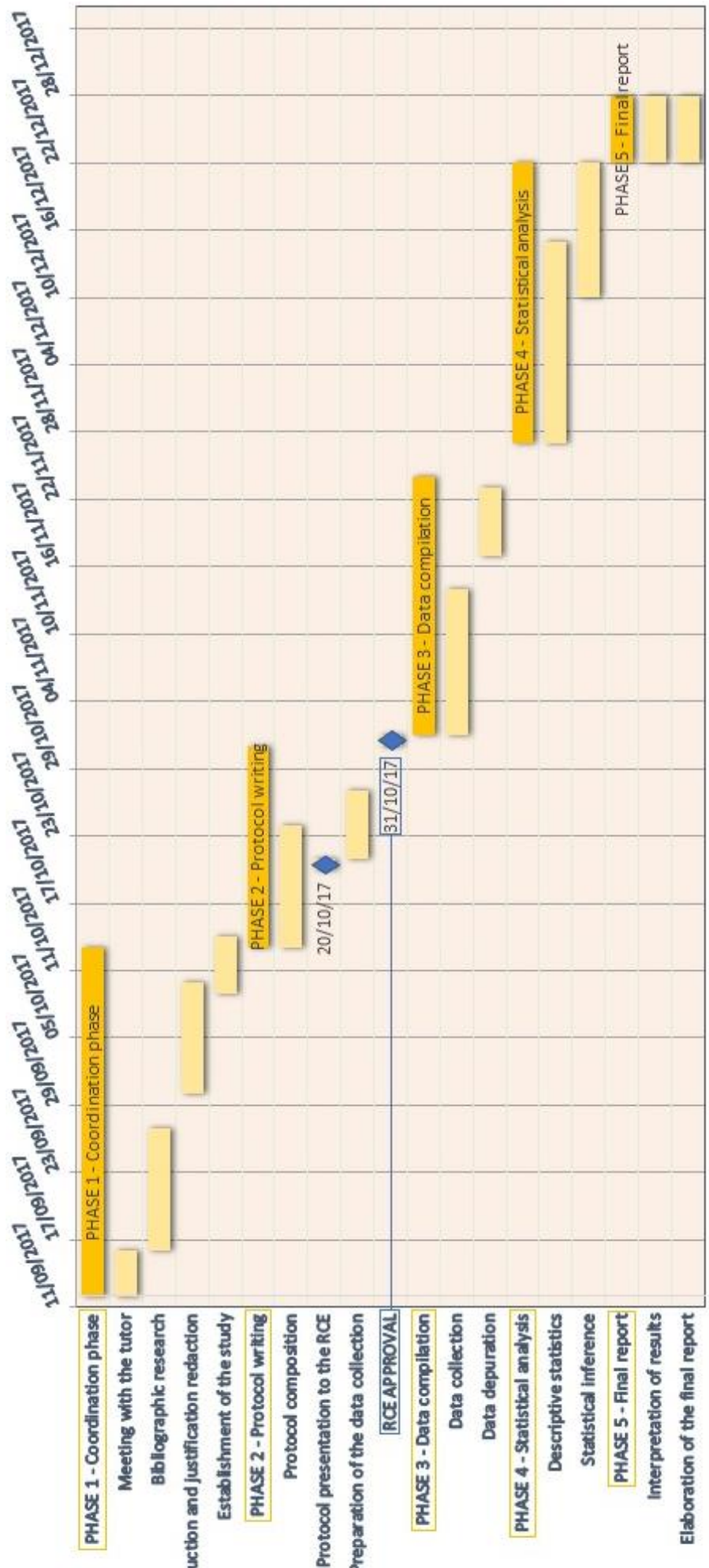
5. **PHASE 5 – RESULTS INTERPRETATION AND FINAL REPORT (1 week):** *[main researcher and FDP tutor]*

   5.1. Interpretation of results: once the statistical analysis had been done, the main researcher has drawn conclusions with the FDP tutor help.

   5.2. Elaboration of the final report: it has been elaborated by the main researcher.

All the phases described above are real, as the following graphic chronogram (on the following page):

STUDY TASKS	STARTING DATE	CLOSING DATE
PHASE 1 - Coordination phase	**12/09/17**	**13/10/17**
Meeting with the tutor	12/09/17	15/09/17
Bibliographic research	16/09/17	29/09/17
Introduction and justification redaction	30/09/17	12/10/17
Establishment of the study	09/10/17	13/10/17
PHASE 2 - Protocol writing	**13/10/17**	**31/10/17**
Protocol composition	13/10/17	20/10/17
Protocol presentation to the RCE	20/10/17	20/10/17
Preparation of the data collection	21/10/17	27/10/17
RCE APPROVAL	31/10/17	31/10/17
PHASE 3 - Data compilation	**01/11/17**	**24/11/17**
Data collection	01/11/17	17/11/17
Data depuration	17/11/17	24/11/17
PHASE 4 - Statistical analysis	27/11/17	22/12/17
Descriptive statistics	27/11/17	15/12/17
Statistical inference	10/12/17	22/12/17
PHASE 5 - Final report	**22/12/17**	**05/01/18**
Interpretation of results	22/12/17	05/01/18
Elaboration of the final report	22/12/17	05/01/18


11/09/2017
17/09/2017
23/09/2017
29/09/2017
05/10/2017
11/10/2017
17/10/2017
23/10/2017
29/10/2017
04/11/2017
10/11/2017
16/11/2017
22/11/2017
28/11/2017
04/12/2017
10/12/2017
16/12/2017
22/12/2017
28/12/2017
PHASE 1 - Coordination phase
Meeting with the tutor
Bibliographic research
Introduction and justification redaction
Establishment of the study
PHASE 2 - Protocol writing
Protocol composition
Protocol presentation to the RCE
20/10/17
Preparation of the data collection
RCE APPROVAL
31/10/17
PHASE 3 - Data compilation
Data collection
Data depuration
PHASE 4 - Statistical analysis
Descriptive statistics
Statistical inference
PHASE 5 - Final report
Interpretation of results
Elaboration of the final report
PHASE 4 - Statistical analysis
PHASE 5 - Final report

14. BIBLIOGRAPHY

1. Suárez-Ortega S, Puente-Fernández A, Santana-Baez S, Godoy-Díaz D, Serrano-Fuentes M, Sanz-Peláez O. Síndrome constitucional: entidad clínica o cajón de sastre. Rev Med Inst Mex Seguro Soc [Internet]. 2013 [cited 2017 Oct 23];51(5):532–5. Available from: http://new.medigraphic.com/cgi-bin/resumen.cgi?IDARTICULO=45297

2. Bouras EP, Lange SM, Scolapio JS. Rational Approach to Patients With Unintentional Weight Loss. Mayo Clin Proc [Internet]. 2001 [cited 2017 Oct 3];76(9):923–9. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0025619611621137

3. Gaddey HL, Holder K. Unintentional Weight Loss in Older Adults. Am Fam Physician [Internet]. 2014 May [cited 2017 Nov 8];89(9):718–22. Available from: http://www.aafp.org/afp/2014/0501/p718.html

4. Pérez Valer I, Gil Aguado A, Robles Marhuenda A, Ríos Blanco JJ. Actitud diagnóstica ante un paciente con síndrome constitucional. JANO [Internet]. 2005 [cited 2017 Oct 23];69(1576):51–6. Available from: http://www.jano.es/ficheros/sumarios/1/69/1576/51/1v69n1576a13079031pdf001.pdf

5. Young P, Finn BC, Bruetman JE, Pellegrini D, Kremer A. Enfoque del síndrome de astenia crónica. Med (Buenos Aires) [Internet]. 2010 [cited 2017 Oct 3];70(3):284–92. Available from: http://www.scielo.org.ar/pdf/medba/v70n3/v70n3a15.pdf

6. Avellaneda Fernández A, Pérez Martín Á, Izquierdo Martínez M, Arruti Bustillo M, Barbado Hernández FJ, de la Cruz Labrado J, et al. Chronic fatigue syndrome: aetiology, diagnosis and treatment. BMC Psychiatry [Internet]. BioMed Central; 2009 Oct 23 [cited 2017 Nov 8];9(Suppl 1):S1. Available from: http://bmcpsychiatry.biomedcentral.com/articles/10.1186/1471-244X-9-S1-S1

7. Robertson RG, Larry Jameson J. Pérdida de peso involuntaria. In: Longo DL, Kasper DL, Larry Jameson J, Fauci AS, Hauser SL, Loscalzo J, editors. Harrison: principios de medicina interna. 18a ed. México, D.F.: McGraw-Hill Interamericana; 2012. p. 641–3.

8. Alibhai SMH, Greenwood C, Payette H. An approach to the management of unintentional weight loss in elderly people. CMAJ [Internet]. 2005 [cited 2017 Sep 23];172(6):773–80. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15767612

9. Braun TP, Marks DL. Pathophysiology and treatment of inflammatory anorexia in chronic disease. J Cachexia Sarcopenia Muscle [Internet]. 2010 [cited 2017 Oct 7];1(2):135–45. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21475703

10. Landi F, Calvani R, Tosato M, Martone AM, Ortolani E, Savera G, et al. Anorexia of Aging: Risk Factors, Consequences, and Potential Treatments. Nutrients [Internet]. 2016 Jan 27 [cited 2017 Oct 7];8(2):69. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26828516

11. Evans WJ, Morley JE, Argilés J, Bales C, Baracos V, Guttridge D, et al. Cachexia: a new definition. Clin Nutr [Internet]. Elsevier; 2008 Dec 1 [cited 2017 Oct 7];27(6):793–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18718696

12. Tuca Rodríguez A, Calsina-Berna A, González-Barboteo J, Gómez-Batiste Alentorn X. Caquexia en cáncer. Med Clin (Barc) [Internet]. 2010 Oct [cited 2017 Sep 23];135(12):568–72. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0025775310006391

13. Hernández Hernández JL, Matorras Galán P, Riancho Moral JA, González-Macías J. Espectro etiológico del síndrome general solitario. Rev Clínica Española. 2002;202(7):367–74.

14. Capell S, Comas P, Piella T, Rigau J, Pruna X, Martínez F, et al. Unidad de diagnóstico rápido: un modelo asistencial eficaz y eficiente. Experiencia de 5 años. Med Clin (Barc) [Internet]. 2004 [cited 2017 Oct 8];123(7):247–50. Available from: http://www.elsevier.es/es-revista-medicina-clinica-2-

articulo-unidad-diagnostico-rapido-un-modelo-13065197

15. Argilés JM, Busquets S, López-Soriano F.J., Figueras M. Fisiopatología de la caquexia neoplásica. Nutr Hosp [Internet]. 2006 [cited 2017 Oct 8];21(supl.3):4–9. Available from: http://scielo.isciii.es/scielo.php?script=sci_arttext&pid=S0212-16112006000600002

16. Boyd AD, Riba M, Arbor A. Depression and Pancreatic Cancer. J Natl Compr Cancer Netw. 2007;5(1):113–6.

17. Massie MJ. Prevalence of Depression in Patients With Cancer. J Natl Cancer Inst Monogr [Internet]. 2004 Jul 1 [cited 2017 Nov 17];2004(32):57–71. Available from: https://academic.oup.com/jncimono/article-lookup/doi/10.1093/jncimonographs/lgh014

18. Zabora J, Brintzenhofeszoc K, Curbow B, Hooker C, Piantadosi S. The prevalence of psychological distress by cancer site. Psychooncology. 2001;10(1):19–28.

19. Griffeth BT, Mehra A. Panic as a harbinger of pancreatic cancer. Psychosomatics [Internet]. 2008;49(6):538–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19122132

20. Passik SD, Roth a J. Anxiety symptoms and panic attacks preceding pancreatic cancer diagnosis. Psychooncology [Internet]. 1999;8(3):268–72. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10390740

21. Castro Alvirena JD, Bravo CV. Protocolo diagnóstico y tratamiento del síndrome constitucional en los pacientes mayores. Medicine (Baltimore) [Internet]. 2014 [cited 2017 Oct 23];11(62):3720–4. Available from: https://nutrigeriatria.files.wordpress.com/2016/02/perdida-de-peso-medicine-2014.pdf

22. Lankisch PG, Gerzmann M, Gerzmann J-F, Lehnick D. Unintentional weight loss: diagnosis and prognosis. The first prospective follow-up study from a secondary referral centre. J Intern Med [Internet]. 2001 Jan 1 [cited 2017 Oct 24];249(1):41–6. Available from: http://doi.wiley.com/10.1046/j.1365-2796.2001.00771.x

23. Bilbao-Garay J, Barba R, Losa-García JE, Martín H, García de Casasola G, Castilla V, et al. Assessing clinical probability of organic disease in patients with involuntary weight loss: a simple score. Eur J Intern Med [Internet]. 2002 Jun 1 [cited 2017 Oct 24];13(4):240–5. Available from: http://www.sciencedirect.com/science/article/pii/S0953620502000328?via%3Dihub

24. Rabinovitz M, Pitlik SD, Leifer M, Garty M, Rosenfeld JB. Unintentional Weight Loss: Retrospective Analysis of 154 Cases. Am J Med. 1986;146(Jan):186–7.

25. Huffman GB. Evaluating and treating unintentional weight loss in the elderly. Am Fam Physician [Internet]. 2002 Feb 15 [cited 2017 Sep 23];65(4):640–50. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11871682

26. Buitrago Ramírez F, Carmona JA, Morales Gabardino JA. Estudio inicial del paciente con síndrome constitucional en atención primaria. FMC Form Médica Contin en Atención Primaria [Internet]. Ediciones Doyma; 2012 May 1 [cited 2017 Oct 17];19(5):268–77. Available from: http://www.fmc.es/es/estudio-inicial-del-paciente-con/articulo/X1134207212402803/

27. Torres Salinas M, Capdevila Morel JA, Armario García P, Montull Morer S. Alternativas a la hospitalización convencional en medicina interna. Med Clin (Barc) [Internet]. 2005 Apr [cited 2017 Oct 8];124(16):620–6. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0025775305718352

28. Franco Hidalgo S, Prieto de Paula JM, Martín Serradilla JI, Martín Carbayo JL. Unidades de diagnóstico rápido o consultas de atención inmediata en medicina interna. Análisis de los primeros 6 meses de funcionamiento en Palencia. Semer - Med Fam [Internet]. 2012 Mar [cited 2017 Oct 8];38(2):126–30. Available from: http://linkinghub.elsevier.com/retrieve/pii/S1138359311004011

29. Chen S-P, Peng L-N, Lin M-H, Lai H-Y, Hwang S-J, Chen L-K. Evaluating probability of cancer among older people with unexplained, unintentional weight loss. Arch Gerontol Geriatr [Internet]. 2010 Feb 1 [cited 2017 Oct 24];50:S27–9. Available from: http://www.sciencedirect.com/science/article/pii/S016749431070008X?via%3Dihub

30. San José Laporte A, Jiménez Moreno X, Ligüerre Casals I, Vélez Miranda MC, Vilardell Tarrés M. Atención especializada ambulatoria rápida de patologías médicas desde un hospital universitario terciario. Consulta de atención inmediata. Rev Clínica Española [Internet]. 2008 Feb 1 [cited 2017 Oct 8];208(2):71–5. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0014256508716783

31. Anderson P, Gual A, Colon J. Alcohol y atención primaria de la salud: informaciones clínicas básicas para la identificación y el manejo de riesgos y problemas [Internet]. Washington, D.C.: Organización Panamericana de la Salud; 2008 [cited 2017 Nov 6]. Available from: http://www.who.int/substance_abuse/publications/alcohol_atencion_primaria.pdf

32. IBM SPSS Software. IBM Analytics [Internet]. 2018 [cited 2018 Jan 21]. Available from: https://www.ibm.com/analytics/data-science/predictive-analytics/spss-statistical-software

33. WMA. The World Medical Association [Internet]. Declaration of Helsinki Medical Research Involving Human Subjects. Ferney-Voltaire: The World Medical Association; 2018 [cited 2018 Jan 21]. Available from: https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/

34. WMA. Declaration of Helsinki .Ethical Principles for Medical Research Involving Human Subjects [Internet]. Ferney-Voltaire: The World Medical Association; 2017 [cited 2018 Jan 21]. Available from: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

35. Protección de Datos de Carácter Personal. Ley Orgánica 15/1999 de 13 de diciembre. Boletín Oficial Del Estado, nº298, (14-12-1999). [Internet]. Available from: https://www.boe.es/buscar/doc.php?id=BOE-A-1999-23750

36. Ley básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica. Ley orgánica 41/2002 de 14 de noviembre. Boletín Oficial Del Estado, nº274, (15-11-2002). [Internet]. Available from: https://www.boe.es/buscar/doc.php?id=BOE-A-2002-22188

37. Torné Cachot J, Gallardo Sánchez C, Perona Pagán M, Puig Ponsico G. Impacto de una unidad de diagnóstico rápido en atención primaria. Atención Primaria. 2011;43(2):105–6.

38. Pérez Vega C, Polvorosa Gómez MA, Rodríguez Ramos C, Rodríguez de Castro Hurtado E. Experiencia en los 2 primeros años de una unidad de diagnóstico rápido en un hospital comarcal. Rev Calid Asist [Internet]. 2017 Mar 1 [cited 2017 Oct 16];32(2):114–5. Available from: http://www.elsevier.es/es-revista-revista-calidad-asistencial-256-articulo-experiencia-los-2-primeros-anos-S1134282X16301051

39. Rubio-Rivas M, Vidaller A, Pujol I Farriols R, Mast R. Unidad de diagnóstico rápido en un hospital de tercer nivel. Estudio descriptivo del primer año y medio de funcionamiento. Rev Clin Esp. 2008;208(11):561–3.

40. Sanclemente Anso C, Capdevila Aguilera C, Castellvi Tudó M, Pujol Farriols R, Corbella Viros X, Salazar Soler A. Unidad de diagnóstico rápido como alternativa al ingreso hospitalario en enfermedades potencialmente graves. In: XI Jornadas de gestión y evaluación de costes sanitarios [Internet]. Valladolid; 2012 [cited 2018 Jan 21]. p. 131–2. Available from: http://bazar.fundacionsigno.com/documentos/proceso-asistencial-del-paciente/unidad-de-diagnostico-rapido-como-alternativa-al-ingreso-hospitalario-en-enfermedades-potencialmente-graves.-valladolid-2012

41. Muñoz Fernández L, Campos Calero A, Ruíz González M, Molina Molina F, López Sánchez M, Yeste

Martin R, et al. El “síndrome constitucional” de nuestro hospital. Rev Clin Española [Internet]. 2014 [cited 2017 Sep 23];214(Espec Congr):1161. Available from: http://www.revclinesp.es/controladores/congresos-herramientas.php?idCongreso=15&idSesion=1363&idComunicacion=15300

42. Wu J-M, Lin M-H, Peng L-N, Chen L, Hwang S-J. Evaluating diagnostic strategy of older patients with unexplained unintentional body weight loss: A hospital-based study. Arch Gerontol Geriatr [Internet]. 2011 Jul 1 [cited 2017 Oct 24];53(1):e51–4. Available from: http://www.sciencedirect.com/science/article/pii/S0167494310002657?via%3Dihub

43. Mateos Andrés M, Muñoz Alonso S, Hernández Pérez G, Fuentes Pardo L, Chimeno Viñas M, Arribas Pérez L, et al. Hallazgos etiológicos en los pacientes con síndrome constitucional estudiados en la unidad de diagnóstico rápido del complejo asistencial de Zamora. Rev Clínica Española [Internet]. 2016 [cited 2017 Oct 8];216(Espec Congr):144. Available from: http://www.revclinesp.es/

44. Geriatric Depression Scale [Internet]. Palo Alto, CA: Aging Clinical Research Center (ACRC); [cited 2017 Nov 12]. Available from: https://web.stanford.edu/~yesavage/GDS.html

15. ANNEXES

ANNEX 1: CAUSES OF INVOLUNTARY WEIGHT LOSS (7)

Cancer Colon Hepatobiliary Hematologic Lung Breast Genitourinary Ovarian Prostate	**Medications** Sedatives Antibiotics Nonsteroidal anti-inflammatory drugs Serotonin reuptake inhibitors Metformin Levodopa Angiotensin-converting enzyme inhibitors Other drugs
Gastrointestinal disorders Malabsorption Peptic ulcer Inflammatory bowel disease Pancreatitis Obstruction/constipation Pernicious anaemia	**Disorders of the mouth and teeth** Caries Dysgeusia **Age-related factors** Physiologic changes Visual impairment Decreased taste and smell Functional disabilities
Endocrine and metabolic Hyperthyroidism Diabetes mellitus Pheochromocytoma Adrenal insufficiency	**Neurologic** Stroke Parkinson's disease Neuromuscular disorders Dementia
Cardiac disorders Chronic ischemia Chronic congestive heart failure	**Social** Isolation Economic hardship
Respiratory disorders Emphysema Chronic obstructive pulmonary disease	**Psychiatric and behavioural** Depression Anxiety Paranoia Bereavement Alcoholism Eating disorders Increased activity or exercise
Renal insufficiency	
Rheumatologic disease	
Infections HIV Tuberculosis Parasitic infection Subacute bacterial endocarditis	**Idiopathic**

ANNEX 2: GERIATRIC DEPRESSION SCALE – SHORT FORM (44)

ENGLISH VERSION		
Choose the best answer for how you have felt over the past week		
1. Are you basically satisfied with your life?	YES	**NO**
2. Have you dropped many of your activities and interests?	**YES**	NO
3. Do you feel that your life is empty?	**YES**	NO
4. Do you often get bored?	**YES**	NO
5. Are you in good spirits most of the time?	YES	**NO**
6. Are you afraid that something bad is going to happen to you?	**YES**	NO
7. Do you feel happy most of the time?	YES	**NO**
8. Do you often feel helpless?	**YES**	NO
9. Do you prefer to stay at home, rather than going out and doing new things?	**YES**	NO
10. Do you feel you have more problems with memory than most?	**YES**	NO
11. Do you think it is wonderful to be alive now?	YES	**NO**
12. Do you feel pretty worthless the way you are now?	**YES**	NO
13. Do you feel full of energy?	YES	**NO**
14. Do you feel that your situation is hopeless?	**YES**	NO
15. Do you think that most people are better off than you are?	**YES**	NO
Answers in **bold** indicate depression. Assign one point for each answer in bold. - **Score > 5 points → suggestive of depression.** - **Score > 10 points → almost always depression.**		

VERSIÓ EN CATALÀ		
Esculli la resposta adequada segons com s'ha sentit vostè la setmana passada.		
1. Està bàsicament, satisfet/a amb la seva vida?	SÍ	**NO**
2. Ha suspès moltes de les seves activitats o interessos?	**SÍ**	NO
3. Sent que la seva vida està buida?	**SÍ**	NO
4. S'avorreix sovint?	**SÍ**	NO
5. Està de bon humor la major part del temps?	SÍ	**NO**
6.Té por de que alguna cosa dolenta li vagi a passar?	**SÍ**	NO
7. Es sent feliç la major part del temps?	SÍ	**NO**
8. Es sent sovint indefens/a?	**SÍ**	NO
9. Prefereix quedar-se a casa, en comptes de sortir i fer coses noves?	**SÍ**	NO
10. Respecte a la seva memòria, sent que té més problemes que la majoria de gent?	**SÍ**	NO
11. Pensa que és meravellós estar viu/viva en aquest momento?	SÍ	**NO**
12. De la forma de com es sent en aquest moment, es sent inútil?	**SÍ**	NO
13. Es sent amb molta energia?	SÍ	**NO**
14. Sent que la seva situació és irremediable?	**SÍ**	NO
15. Pensa que la majoria de les persones estan en millors condicions que vostè?	**SÍ**	NO
Les respostes en negreta indiquen depressió. Assigni 1 punt per cada resposta en negreta. - **Puntuació > 5 punts → suggestiu de depressió.** - **Puntuació > 10 punts → casi sempre indicador de depressió.**		

ANNEX 3: DATA COLLECTION FORM

Data collection

*Required

1. **Medical history code (number)** *

2. **Referral source** *
Mark only one oval.
- Primary Health Care
- Outpatient care facilities
- Emergency department
- Hospital inpatient care

3. **Gender** *
Mark only one oval.
- Man
- Woman

4. **Age (years)** *

5. **Smoking** *
Mark only one oval.
- Smoker
- Ex-smoker (>10 pack-years)
- Non-smoker or <10 pack-years

6. **Alcoholism** *
Mark only one oval.
- Yes
- No

7. **History of functional pathology** *
Mark only one oval.
- Yes
- No

8. **Clinical impression** *
Mark only one oval.
- Functional
- Organic

9. **General appearance**
Mark only one oval.
- Good general aspect
- Bad general aspect

10. **Weight loss (kg/month)** *

Laboratory data (1rst VISIT)

11. **ESR (erythrocyte sedimentation rate)** *

12. **Haemoglobin** *

13. **MCH (Mean corpuscular haemoglobin)** *

14. **MCV (Mean corpuscular volume)** *

15. **WBC (white blood cell)** *

16. **Platelet count** *

17. **INR (international normalized ratio)** *

18. **Glomerular filtrate** *

19. **Cholesterol** *

20. **Total bilirubin** *

21. **SGOT** *

22. **SGPT** *

23. **GGT** *

24. **LDH** *

25. **Alkaline phosphatase** *

26. **Albumin** *

27. **C-reactive protein** *

28. **Urinalysis** *
Mark only one oval.
- Pathological
- Non-pathological
- Test not realized

29. **Chest radiography** *
Mark only one oval.
- Pathological
- Non-pathological
- Test not realized

30. **Abdominal echography** *
Mark only one oval.
- Pathological
- Non-pathological
- Test not realized

Complementary studies

31. **Test 1** *
Mark only one oval.
- Thoracic CT
- Abdominal CT
- Thoracic/Abdominal CT
- Other CT (cranial)
- Bone scan
- Bronchoscopy
- Gastroscopy
- Colonoscopy
- Echocardiogram
- Any test
- MRI
- Biopsy
- Peritoneal fluid (paracentesis)
- Temporal artery biopsy
- Wrist radiograph
- Knee radiograph
- Urease test
- MR cholangiopancreatography
- Renal/bladder echography

32. **Test 2**
Mark only one oval.
- Thoracic CT
- Abdominal CT
- Thoracic/abdominal CT
- Other CT (cranial)
- Bone scan
- Bronchoscopy
- Gastroscopy
- Colonoscopy
- Echocardiogram
- MRI
- Biopsy
- Any test
- Wrist radiograph
- Knee radiograph
- EMG
- Hepatic FNA
- Lymph node dissection
- Liver biopsy
- Pleural fluid

33. **Test 3**
Mark only one oval.

- Thoracic CT
- Abdominal CT
- Thoracic/abdominal CT
- Other CT (cranial)
- Bone scan
- Bronchoscopy
- Gastroscopy
- Colonoscopy
- Echocardiogram
- MRI
- Biopsy
- Any test
- Pericardial fluid
- Mammography
- Prostatic biopsy
- Oesophageal manometry

34. **Test 4**
Mark only one oval.

- Thoracic CT
- Abdominal CT
- Thoracic/abdominal CT
- Other CT
- Bone scan
- Bronchoscopy
- Gastroscopy
- Colonoscopy
- Echocardiogram
- MRI
- Biopsy
- Any test
- Pleural fluid

35. **Test 5**
Mark only one oval.

- Pleural biopsy

36. **Test 6**
Mark only one oval.

- PPD skin test

Test significance

37. **Among the tests performed, were any of them essential for the diagnosis?** *
Mark only one oval.

- Yes *Skip to question 38.*
- No *Skip to question 40.*

If the answer was "Yes"...

38. **What test?** *
Mark only one oval.

- Blood analysis
- Thoracic CT
- Abdominal CT
- Thoracic/abdominal CT
- Other CT
- Bone scan
- Bronchoscopy
- Gastroscopy
- Colonoscopy
- Echocardiogram
- MRI
- Biopsy
- Any test
- Abdominal echography
- Chest radiography
- Paracentesis
- MR cholangiopancreatography
- Liver biopsy
- Bladder/vesical echography

Why was the test essential to get the diagnosis?

39. *
Mark only one oval.

- By confirming organic pathology
- By ruling out organic pathology

Final diagnosis

40. **Final diagnosis** *
Mark only one oval.

- ◯ Cancer *Skip to question 41.*
- ◯ Psychiatric diseases *Skip to question 43.*
- ◯ Digestive diseases *Skip to question 44.*
- ◯ Endocrine diseases *Skip to question 45.*
- ◯ Rheumatic diseases *Skip to question 46.*
- ◯ CS of unknown aetiology *Skip to question 53.*
- ◯ Infectious disease *Skip to question 47.*
- ◯ Haemathological diseases
- ◯ Neurological diseases *Skip to question 48.*
- ◯ Renal disease *Skip to question 49.*
- ◯ Drugs - toxics *Skip to question 50.*
- ◯ Vascular disease *Skip to question 51.*
- ◯ Lung disease
- ◯ Urological disease *Skip to question 52.*
- ◯ Advanced heart failure *Skip to question 53.*

Cancer

41. **Type of cancer** *
Mark only one oval.

- ◯ Lymphoma
- ◯ Renal
- ◯ Gastric
- ◯ Colon
- ◯ Uterus
- ◯ Lung
- ◯ Pancreatic
- ◯ Prostatic
- ◯ M1 without primary tumour
- ◯ Ovarian
- ◯ vesical
- ◯ Digestive? (no time to complete the study)
- ◯ Breast
- ◯ Retroperitoneal mass (primary tumour or metastasis)

42. **Metastasis at the time of diagnosis** *
Mark only one oval.

- ◯ Yes
- ◯ No

Skip to question 53.

Psychiatric diseases

43. **Psychiatric diagnosis** *
Mark only one oval.

- ◯ Depression - Anxiety
- ◯ Bipolar disorder (depressive episode)

Skip to question 53.

Digestive diseases

44. **Diagnosis - digestive system** *
Mark only one oval.

- ◯ Peptic disease
- ◯ Chronic inflammatory disease
- ◯ Lactose intolerance
- ◯ Chronic diarrhoea
- ◯ Cholestasis
- ◯ Intussusception
- ◯ Oesophageal motility disorder
- ◯ Barrett oesophagus
- ◯ Gastritis

Skip to question 53.

Endocrine diseases

45. **Diagnosis - endocrine system** *
Mark only one oval.

- ◯ Hyperthyroidism
- ◯ Hypothyroidism
- ◯ Diabetes mellitus

Skip to question 53.

Rheumatic disease

46. **Diagnosis - rheumatic/autoimmune diseases** *
Mark only one oval.

- ◯ Polymyalgia rheumatica
- ◯ Rheumatoid arthritis
- ◯ Vasculitis
- ◯ Sarcoidosis
- ◯ Lupus
- ◯ Giant cell arteritis

Skip to question 53.

Infectious disease

47. **Infection diagnosis** *
Mark only one oval.

- ◯ Urinary tract infection
- ◯ Tuberculosis
- ◯ HIV infection
- ◯ Bronchiectasis infection

Skip to question 53.

Neurological diseases

48. **Neurological diagnosis** *
Mark only one oval.

- ◯ Polyneuropathy
- ◯ Dementia
- ◯ Myopathy
- ◯ Parkinson

Skip to question 53.

Renal diseases

49. **Diagnosis - renal diseases** *
Mark only one oval.

- ◯ Hydronephrosis
- ◯ Glomerulonephritis

Skip to question 53.

Drugs - toxics

50. **What drug or toxic is responsible of the CS?**

Skip to question 53.

Vascular diseases

51. **Diagnosis - vascular diseases** *
Mark only one oval.

- ◯ Abdominal aortic aneurysm

Urological diseases

52. **Diagnosis - urological diseases** *
Mark only one oval.

- ◯ Obstructive uropathy

Skip to question 53.

Timings

53. **Admission need** *
Mark only one oval.

- ◯ Yes
- ◯ No

54. **Referral - RDU (days)** *

55. **RDU - Diagnosis (days)** *

56. **Nº of visits**

57. **Test request - medical report (days)** *

58. **Medical report - next visit (days)**

59. **Death in cancer context** *
Mark only one oval.

- ◯ Yes *Skip to question 60.*
- ◯ No *Skip to question 61.*
- ◯ Not cancer *Stop filling out this form.*

Cancer diagnosis - death

60. **days** *

Stop filling out this form.

Cancer diagnosis - nowadays

61. **days** *

Powered by Google Forms

ANNEX 4: RESEARCH PROTOCOL PRESENTED TO THE RESEARCH ETHICS COMMITTEE

AVALUACIÓ DEL FUNCIONAMENT I RENDIMENT D'UNA UNITAT DE DIAGNÒSTIC RÀPID EN EL CONTEXT DEL SÍNDROME TÒXIC

Treball de final de grau

Autora: Isabel Depoorter
Tutor: Xavier Pla Salas

1. INTRODUCCIÓ

El **síndrome tòxic (ST)**, o també conegut com a síndrome constitucional, és un quadre clínic constituït per astènia, anorèxia i pèrdua de pes. La pèrdua de pes (manifestació més significativa de totes 3) ha de ser una disminució involuntària de mínim el 5% de la pes corporal en 6 mesos (1).

Aquest quadre clínic pot acompanyar-se per simptomatologia inespecífica: febrícula, mal de cap, miàlgies, diaforesis, etc. Normalment, les 3 manifestacions del ST (astènia, anorèxia i pèrdua de pes) coexisteixen, però pot ocórrer que el pacient només en presenti una o dues.

Hi ha un ampli espectre de malalties que poden originar el síndrome tòxic, però es solen diferenciar entre causes orgàniques i causes funcionals (1,4). Els tumors són les principals causes orgàniques, seguit pels trastorns gastrointestinals, i per últim, múltiples malalties cròniques (quan aquestes arriben en situacions de màxim deteriorament). Per altra banda, tenim les causes funcionals, que poden arribar a ser una de les causes més freqüents (8). El síndrome ansiós-depressiu és el més destacat entre les malalties d'origen psiquiàtric. Aquest sol tenir una presentació més larvada i no clara, i per això és necessari fer una anamnesi detallada i exhaustiva, ja que molts casos poden passar desapercebuts.

Les dades epidemiològiques del ST depenen de les característiques de la població estudiada, del nivell d'atenció sanitària en què els pacients són atesos i de quines manifestacions del ST presenten (21).

D'aquesta manera, la coexistència de les 3 manifestacions del ST difereix del 3,4% dels pacients visitats en un servei de medicina interna (13) al 11% corresponent a un altre hospital.

Pel que fa al síndrome tòxic en el context de càncer, la seva prevalença varia des del 40% dels pacients en fase diagnòstica al 70-80% en casos avançats. La prevalença de ST en càncer també varia segons l'origen del tumor primari: 83-85% en neoplàsies gàstriques i pancreàtiques; 54-60% en pulmó, pròstata i neoplàsia de colon, i 32-48% en càncer de mama, sarcoma, limfoma i leucèmies (12). L'esperança de vida en pacients oncològics *amb ST* és significativament menor que els que no en presenten i pot arribar ser la causa de mort en més d'un 20% en aquests pacients.

L'objectiu principal davant d'un pacient amb ST és trobar-ne la causa i tractar-la. Considerant totes les possibles causes del ST, la que crea més preocupació és el càncer, per la seva especial mala evolució en aquests casos. Per això mateix, l'estudi d'un pacient amb ST està encarat a descartar com més ràpid possible l'existència d'una neoplàsia subjacent encara no diagnosticada (4).

Molt sovint, els dispositius sanitaris encarregats d'estudiar i trobar la causa del ST en un pacient són les Unitats de Diagnòstic Ràpid (UDR) dels serveis de medicina interna (27), com és el cas de UDR del Hospital de dia de l'Hospital Universitari de Vic (HUV). En general, les UDR reben pacients amb diferents tipus de quadres clínics que necessiten rapidesa assistencial ja que les malalties subjacents causants poden ser potencialment greus. Entre els altres quadres clínics que arriben a les UDR, a part del síndrome tòxic tenim: pacients amb adenopaties, febres d'origen desconegut, anèmies o malalties autoimmunes sistèmiques.

L'objectiu d'una UDR és reduir els retards diagnòstics, millorar la coordinació amb els serveis d'Atenció Primària (AP) i finalment, reduir les hospitalitzacions (28).

El funcionament de la UDR del Hospital de dia del HUV està basat en oferir una primera consulta el més ràpid possible i realitzar les proves necessàries amb caràcter preferent. Els pacients poden venir derivats des dels centres d'AP, d'urgències o de consultoris d'altres especialitats.

És imprescindible que els especialistes de cada servei (AP, metges de la UDR, metges que realitzen proves) es coordinin bé entre ells, per tal d'aconseguir el màxim rendiment en benefici del pacient.

Fins avui dia, dins la literatura mèdica, trobem per una banda, estudis descriptius que valoren la incidència de les diferents etiologies que cursen amb ST, i per altra banda estudis que avaluen el funcionament de les UDR de manera global, incloent tots motius de derivació (anèmia, limfoadenopaties, febre d'origen desconegut, síndrome tòxic...). Ara bé, cap estudi ha avaluat específicament el funcionament d'una UDR pel que fa al síndrome tòxic, i aquest últim, justament és un dels motius més freqüents de consulta en una UDR (14,30). *Per això mateix, aprofitant que la UDR del Hospital de dia del HUV es va obrir l'any 2015, hem vist convenient poder realitzar aquesta avaluació específica del síndrome tòxic en el seu servei.*
Avaluar la UDR de ST podrà ajudar a detectar errors en la gestió dels pacients i permetrà millorar la detecció de càncer i/o malalties potencialment greus en aquesta població.
Per altra banda, permetrà generar hipòtesis etiològiques que donaran pas a desenvolupar nous estudis, tals com l'estratificació del risc d'aquests pacients quan arriben a la UDR i analitzar els factors associats a la supervivència dels pacients diagnosticats per càncer.

2. HIPÒTESI I OBJECTIUS

a. OBJECTIUS

- **Avaluar el funcionament del servei d'UDR pel que fa al síndrome tòxic de l'Hospital de dia de l'Hospital universitari de Vic.**
- **Conèixer les malalties responsables del síndrome tòxic en la comarca d'Osona.**
- Establir quina és la eina diagnòstica més utilitzada per arribar al diagnòstic causant del síndrome tòxic.

b. HIPÒTESIS

- **El servei d'UDR de síndrome tòxic del HdiaMI és útil i eficaç a l'hora d'agilitzar i arribar al diagnòstic final, equiparant-se a altres serveis UDR d'altres hospitals.**
- **Les malalties responsables del síndrome tòxic en la comarca d'Osona no difereixen de les exposades en altres estudis similars.**
- L'eina diagnòstica més utilitzada és el TC, tant per descartar com confirmar una patologia orgànica.

3. METODOLOGIA

a. DISSENY DE L'ESTUDI

Es tracta d'un estudi descriptiu, observacional i retrospectiu dels pacients consultats a la UDR per síndrome tòxic entre l'1 de maig del 2015 i el 31 d'abril del 2017.

b. POBLACIÓ D'ESTUDI

Aquest estudi es basa en tots els pacients visitats a la UDR per síndrome tòxic en el HdiaMI del Hospital General de Vic entre l'1 de maig del 2015 i el 31 d'abril del 2017.

c. CRITERIS D'INCLUSIÓ I EXCLUSIÓ

Criteris inclusió

→ Pacient derivats a la UDR per síndrome tòxic entre el 1 de maig del 2015 i el 31 d'abril del 2017.

Com a síndrome tòxic entenem la presència d'astènia, anorèxia i pèrdua de pes superior al 5% del pes corporal en els últims 6 mesos. La pèrdua de pes ha estat acceptada si s'ha documentat a la història clínica, tant per estimació numèrica del pes perdut (kg), per proporció (>5% del pes corporal en últims 6 mesos), o constatat per familiar o amic.

El pacient ha hagut de ser derivat des d'Atenció Primària, Urgències o consultes externes de l'hospital. La petició de consulta ha d'haver-se fet per via telefònica, via e-mail o derivació interna de URG o CCEE.

Criteris exclusió:

→ Pacients que eren derivats a la UDR per síndrome tòxic ja acompanyat d'una malaltia de diagnòstic coneguda prèviament (mèdica o psiquiàtrica).

→ Pacients que intentaven perdre pes voluntàriament, per dietes aprimants com per exercici físic elevat.

→ Pacients que havien pres diürètics en els 3 mesos anteriors a l'inici del quadre.

→ Pacients que eren derivats Circuits de Diagnòstic Ràpid (CDR) específics d'altres especialitats, com el CDR de neoplàsia de mama, CDR de neoplàsia de colon, CDR de neoplàsia de pulmó.

d. GRANDÀRIA MOSTRAL I JUSTIFICACIÓ

La grandària mostral correspondrà a tots els pacients (N) que hagin estat derivats i atesos per la UDR del Hospital de Dia de Vic entre el les dades establertes (01/05/2015 – 31/04/2017).

e. DESCRIPCIÓ DE LES ACTIVITATS QUE ES REALITZARAN.

1r. RECOLLIDA DE DADES
Es recolliran tots els pacients derivats a la UDR per síndrome tòxic entre les dates establertes (01/05/2015 – 31/04/2017). A partir de la història clínica (HC) de cada pacient, se'n farà la recollida de dades que interessen per fer l'estudi.
2n. ANÀLISI ESTADÍSTIC
Es realitzarà un anàlisi descriptiu a través de les dades recollides, on s'avaluarà: el funcionament de la UDR de síndrome tòxic al HdiaMI, el comportament del síndrome tòxic en els pacients, i les incidències dels diagnòstics causants del quadre clínic. Es buscarà associació entre dades analítiques o clíniques recollides i el retard diagnòstic del síndrome tòxic.
3r. DISCUSSIÓ
Un cop recollits els resultats de l'anàlisi estadístic, se'n farà una avaluació objectiva per poder determinar la utilitat de la UDR de síndrome tòxic. Discutir si hi hagut errors sistemàtics o de procediment durant el procés assistencial d'aquests pacients, valorant el retard diagnòstic i la rendibilitat del dispositiu.

f. DESCRIPCIÓ DE LES DETERMINACIONS I MESURES DE L'ESTUDI (procés de recollida de dades, tècniques de mesura).

La recollida de dades es realitzarà a través de les històries clíniques dels pacients visitats amb el diagnòstic inicial de síndrome tòxic. Les variables a recollir són:

- Dades sociodemogràfiques: edat i sexe.
- Característiques assistencial d'UDR:
  - Procedència de la derivació (AP, CCEE, URG).
  - Dies transcorreguts entre derivació i primera visita amb UDR
  - Dies transcorreguts entre primera visita i diagnòstic final de la malaltia causant del síndrome tòxic.

    - Dies transcorreguts entre la petició d'una prova durant el procés assistencial i l'informe de la prova.

- Dades recollides durant primera visita amb UDR del HdiaMI:
    - Hàbits tòxics: tabac i hàbit enòlic.
    - Antecedents patològics: presència d'antecedents de patologia funcional i antecedents de malalties prèvies (hipertensió, diabetis mellitus, altres.).
    - Exploració física: impressió de la possible malaltia causant del quadre tòxic segons ull clínic (funcional o orgànica), estat general del pacient segons ull clínic (bon estat general o mal estat general).
    - Paràmetres de laboratori de l'analítica realitzada dia de la visita a UDR:
        - Hemograma: hemoglobina, hemoglobina corpuscular mitja (HCM), volum corpuscular mig (VCM), leucòcits i plaquetes
        - Coagulació: INR
        - Bioquímica: albúmina, colesterol total, fosfatasa alcalina (FA), bilirubina total, transaminases (glutamat-oxalacetat transaminasa – GOT, glutamat-piruvat transaminasa – GPT, gamma-glutamil-transferasa – GGT) i lactat deshidrogenasa (LDH)
        - Funció renal: filtrat glomerular (FG) i anormalitats a l'anàlisi d'orina (presència d'hematúria, leucocitària, proteïnúria o sediment)
        - Reactants de fase aguda: (*polymerase chain reaction* – PCR i velocitat de sedimentació globular – VSG).
    - Proves diagnòstiques: radiografia de tòrax, ecografia i altres proves complementàries.
- Diagnòstic final causant del síndrome tòxic.
- Necessitat d'ingrés degut al quadre tòxic.
- Mortalitat en context de neoplàsia maligna, i quant temps (dies) passa entre diagnòstic de neoplàsia maligna i exitus.

  La base de dades recollida es sotmetrà a un procés de dissociació de tal manera que la identitat del pacient quedi deslligada de les dades de caràcter personal o la seva associació no es pugui fer.

g. DESCRIPCIÓ DELS MECANISMES DE CONTROL DE QUALITAT: Normes de control de qualitat dels diferents components de la investigació.

   Per garantir que la recollida de dades es fa de manera objectiva i homogènia, la farà una mateixa persona. Aquesta recollida de dades estarà sistematitzada a través d'un formulari de Google form, assegurant així que totes les dades s'obtindran de la mateixa manera per tothom.

h. DESCRIPCIÓ DE L'ESTUDI PILOT.

   Aquest estudi no necessita d'un estudi pilot.

i. PLA D'ANÀLISI ESTADÍSTIC.

   Després de revisar les dades prèviament al anàlisis, en busca de valors no habituals o il·lògics, o d'errors de transcripció o codificació, el pla estadístic es divideix en dues parts:

   I. <u>Estadística descriptiva:</u> descriure els subjectes estudiats per tal d'avaluar l'adequació de la mostra respecte el problema plantejat, conèixer en quin tipus de subjectes hem obtingut el resultat i poder interpretar així correctament les conclusions de l'estudi.

Es realitzaran resums numèrics en taules de freqüència i representacions gràfiques de les dades obtingudes, per facilitar-ne un anàlisi visual. Segons el tipus de variables, es faran servir diagrames de barres i/o sectorials (per variables qualitatives o quantitativa discretes), o histogrames (per variables quantitatives continues).

La variable principal d'estudi és el temps transcorregut entre la primera visita a la UDR i el diagnòstic final de ST, sent una distribució asimètrica. Al ser una distribució asimètrica es calcularà la mediana com mesura de localització i el rang interquartílic com mesura de dispersió.

II. Estadística inferencial: a través de contrastos d'hipòtesis. La probabilitat màxima de que els resultats diferents observats entre els dos grups puguin ser degut simplement a l'atzar s'assumeix que és del 5%.

Per poder demostrar o no la associació entre les dues variables es generarà un valor de *p,* a través d'uns tests no paramètrics. Es contrastarà la variable principal per categories de les variables restants. Quan la covariable tingui 2 categories s'utilitzarà el test de U-Mann-Whitney per contrastar la hipòtesi nul·la. Si té >2 categories, s'utilitzarà el test de Kruskal-Wallis.

4. PLA DE TREBALL

Preparació

Fase 0 → 3 setmanes.

1. Reunió amb el tutor del Treball de Final de Grau (Xavier Pla Salas) per decidir tema a tractar.
2. Recerca bibliogràfica sobre el síndrome tòxic i les unitats de diagnòstic ràpid.
3. Definició dels objectius del treball i redacció de la introducció.

Fase 1 → 2 setmanes

1. Redacció del protocol destinat al CEIC de l'Hospital Universitari de Vic. S'hi defineixen les variables, la mostra, la metodologia i el pla estadístic previst.
2. Preparació de la recollida de dades.

Recollida de dades – UN COP EL CEIC HAGI APROVAT EL PROTOCOL

Fase 2 → 2 setmanes

1. Recollida de totes les dades amb posterior anonimització d'aquestes.
2. Depuració de la base de dades perquè ens permeti fer els càlculs estadístics.

Anàlisi de les dades i resultats

Fase 3 → 2 setmanes

1. Estadística descriptiva a partir de la base de dades obtinguda.
2. Estadística inferencial a partir de la base de dades obtinguda.
3. Anàlisi dels resultats i conclusions.

5. PRESSUPOST

El cost final d'aquest estudi és de 0€.

6. BIBLIOGRAFIA

1. Suárez-Ortega S, Puente-Fernández A, Santana-Baez S, Godoy-Díaz D, Serrano-Fuentes M, Sanz-Peláez O. Síndrome constitucional: entidad clínica o cajón de sastre. Rev Med Inst Mex Seguro Soc [Internet]. 2013 [cited 2017 Oct 23];51(5):532–5. Available from: http://new.medigraphic.com/cgi-bin/resumen.cgi?IDARTICULO=45297

2. Pérez Valer I, Gil Aguado A, Robles Marhuenda A, Ríos Blanco JJ. Actitud diagnóstica ante un paciente con síndrome constitucional [Internet]. [cited 2017 Oct 23]. Available from: http://www.jano.es/ficheros/sumarios/1/69/1576/51/1v69n1576a13079031pdf001.pdf

3. Alibhai SMH, Greenwood C, Payette H. An approach to the management of unintentional weight loss in elderly people. C Can Med Assoc J [Internet]. 2005 Mar 15 [cited 2017 Oct 3];172(6):773–80. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15767612

4. Castro Alvirena JD, Bravo CV. Protocolo diagnóstico y tratamiento del síndrome constitucional en los pacientes mayores. Medicine (Baltimore) [Internet]. 2014 [cited 2017 Oct 23];11(62):3720–4. Available from: https://nutrigeriatria.files.wordpress.com/2016/02/perdida-de-peso-medicine-2014.pdf

5. Hernández Hernández JL, Matorras Galán P, Riancho Moral JA, González-Macías J. Espectro etiológico del síndrome general solitario. Rev Clínica Española. 2002;202(7):367–74.

6. Tuca Rodríguez A, Calsina-Berna A, González-Barboteo J, Gómez-Batiste Alentorn X. Caquexia en cáncer. Med Clin (Barc) [Internet]. 2010 Oct [cited 2017 Sep 23];135(12):568–72. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0025775310006391

7. Torres Salinas M, Capdevila Morel JA, Armario García P, Montull Morer S, Hospitales de Cataluña grupo de trabajo de los S de MI de los. Alternativas a la hospitalización convencional en medicina interna. Med Clin (Barc) [Internet]. 2005 Apr [cited 2017 Oct 8];124(16):620–6. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0025775305718352

8. Franco Hidalgo S, Prieto de Paula JM, Martín Serradilla JI, Martín Carbayo JL. Unidades de diagnóstico rápido o consultas de atención inmediata en medicina interna. Análisis de los primeros 6 meses de funcionamiento en Palencia. Semer - Med Fam [Internet]. 2012 Mar [cited 2017 Oct 8];38(2):126–30. Available from: http://linkinghub.elsevier.com/retrieve/pii/S1138359311004011

9. Capell S, Comas P, Piella T, Rigau J, Pruna X, Martínez F, et al. Unidad de diagnóstico rápido: un modelo asistencial eficaz y eficiente. Experiencia de 5 años. Med Clin (Barc) [Internet]. 2004 [cited 2017 Oct 8];123(7):247–50. Available from: http://www.elsevier.es/es-revista-medicina-clinica-2-articulo-unidad-diagnostico-rapido-un-modelo-13065197

10. San José Laporte A, Jiménez Moreno X, Ligüerre Casals I, Vélez Miranda MC, Vilardell Tarrés M. Atención especializada ambulatoria rápida de patologías médicas desde un hospital universitario terciario. Consulta de atención inmediata. Rev Clínica Española [Internet]. 2008 Feb 1 [cited 2017 Oct 8];208(2):71–5. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0014256508716783

ANNEX 5: CEIC APPROVAL

FORES

Informe del CEIC d'aprovació de l'estudi

Dr. Eduardo Kanterewicz, President del Comitè Ètic d' Investigació Clínica de la Fundació d'Osona per a la Recerca i l'Educació Sanitàries (FORES)

Faig constar

Que d'acord amb els antecedents documentals que existeixen en els arxius del CEIC,

ISABEL DEPOORTER RUELLE

consta en qualitat d'investigador/a principal del projecte juntament amb el seu tutor

XAVIER PLA SALAS

del projecte: **Avaluació del funcionament i rendiment d'una unitat de diagnòstic ràpid en el context del síndrome tòxic**

Codi CEIC 2017953 Codi Propi PR184

Va ser aprovat per aquest CEIC el 31/10/2017

Promotor **CONSORCI HOSPITALARI DE VIC**

FORES
COMITÈ ÈTICA
D'INVESTIGACIÓ CLÍNICA
C. Francesc Pla «El Vigatà», 1
08500 VIC

Eduardo Kanterewicz Binstock

Vic, 27 de novembre de 2017

ANNEX 6: CONTRACT SIGNED BY THE MAIN RESEARCHER

This contract states the required commitment of the main researcher during the access and processing of patients' personal data.

En Pere Soley Bach, amb DNI [redacted] actuant com a Gerent de l'entitat Consorci Hospitalari de Vic amb CIFQ5856102H i domicili a Vic, al carrer Francesc Pla "el Vigatà" núm.1 , com a responsable del fitxer,

i

Na Isabel Depporter Ruelle amb DNI 41531443K actuant com a Estudiant de Medicina de la Universitat de Girona, amb i domicili a Girona, com a encarregat de tractament,

Amb l'objectiu d'establir el contracte d'encarregat de tractament de l'entitat UdG (en endavant, l'encarregat del tractament), respecte la realització de la monitorització de l'estudi "Avaluació del funcionament i rendiment d'una unitat de diagnòstic ràpid en el context del síndrome tòxic" per a la qual es requereix l'accés i/o tractament de les dades de caràcter personal del Consorci Hospitalari de Vic;

D'acord amb la legislació vigent respecte a la Protecció de Dades de Caràcter Personal (LOPD 15/1999, de 13 de desembre, i R.D. 1720/2007, de 21 de desembre), s'acorden els següents pactes:

1. L'encarregat del tractament guardarà sigil sobre les dades de caràcter personal de les que tingui coneixement per raó de les prestacions objecte del present contracte. Tot el personal de l'encarregat del tractament que accedeixi i/o tracti dades de caràcter personal resta subjecte al secret professional i deure de confidencialitat, obligació que perdura un cop finalitzada la prestació de serveis.

   La vulneració per part de l'encarregat de tractament o del personal al seu servei del deure de confidencialitat sobre les esmentades dades o de qualsevol altra obligació derivada de la legislació de protecció de dades de caràcter personal, serà causa de resolució del present contracte, sens perjudici de les accions de responsabilitat civil o penal que s'escaiguin.

2. Per al tractament de les dades, l'encarregat del tractament es sotmetrà en tot moment a les instruccions del responsable del Consorci Hospitalari de Vic. En concret, l'encarregat del tractament es compromet a:

   A. No aplicar ni utilitzar les dades de caràcter personal a les que tingui accés en l'exercici de les funcions que li han estat encarregades amb finalitats diferents a les d'aquest contracte.

   B. No cedir les dades ni revelar-les a terceres persones. La possibilitat de subcontractació a tercers per part de l'encarregat del tractament precisa en tot cas d'autorització expressa del Consorci Hospitalari de Vic, amb excepció del que es disposa a l'article 21.2 RD 1720/2007, de 21 de desembre.

   C. Un cop complerta la prestació contractual, els suports i documents que continguin dades de caràcter personal hauran de destruir-se o retornar-se a al Consorci Hospitalari de Vic, o bé a qui s'hagi designat al contracte. No procedeix la destrucció de les dades quan existeixi una previsió legal que exigeixi la seva conservació, l'encarregat del tractament conservarà degudament aquestes dades bloquejades mentre poguessin derivar-se'n responsabilitats.

   D. En cas que l'encarregat del tractament destini les dades a una altra finalitat, les comuniqui o les utilitzi incomplint les estipulacions del contracte, es considerarà responsable del tractament i respondrà de les infraccions en què hagi incorregut personalment.

E. En qualsevol cas, l'accés i tractament de les dades per part de l'encarregat del tractament està sotmès a les mesures de seguretat de la normativa en protecció de dades.

F. El personal de l'encarregat del tractament que tingui accés als recursos del sistema d'informació del responsable del fitxer es troba subjecte al compliment de les mesures de seguretat del document de seguretat del Consorci Hospitalari de Vic. S'adjunta al present document les mesures de seguretat a complir per part de l'encarregat del tractament

G. Quan el servei prestat per l'encarregat del tractament sigui en els seus locals, cal que elabori el corresponent document de seguretat, identificant el tractament i responsable, així com incorporant les mesures de seguretat requerides.

El Consorci Hospitalari de Vic requereix a l'encarregat del tractament que anualment aporti un certificat extern o còpia de l'informe de l'auditoria, pel qual s'acrediti el compliment de les mesures de seguretat.

I de conformitat amb l'establert en aquest document, signen com a representants d'ambdues empreses,

Vic, 9 de novembre de 2017

Representant del Consorci Hospitalari de Vic

Pere Soley Bach

Representant de l'Encarregat del tractament

Isabel Depoorter Ruelle

ANNEX 7: SPECIFIC SUMMARY STATISTICS

Table 7. Assistance activity according to the final diagnosis

	Referral – RDU (days)		RDU – Diagnosis (days)		Test request – medical report (days)		Medical report – next visit (days)		Nº of visits (N)	
	Mean	*Median*	*Mean*	*Median*	*Mean*	*Median*	*Mean*	*Median*	*Mean*	*Median*
Cancer	3,4 (3,8)	2 [2 – 4]	12 (18,4)	5 [0 – 17]	9,1 (11,7)	4,5 [0 – 14,5]	2,3 (2,9)	1 [0 – 3,5]	1,7 (0,8)	2 [1 – 2]
Psychiatric diseases	4,6 (2,5)	4 [3 – 6,5]	8,3 (22)	0 [0 – 4]	18,8(23, 4)	12 [2 – 23]	11,7 (8,6)	8 [7 – 15]	1,9 (0,7)	2 [1 – 2]
Digestive diseases	4,5 (3,3)	4,5 [1,5 – 6]	11,4 (10,6)	10 [2 - 17]	10,4 (9,2)	8,5 [2,5 – 17,5]	8,1 (7,6)	8,5 [0,5 – 13]	2,2 (1,3)	2 [1 – 2,5]
CS of unknown aetiology	3 (1,5)	3 [2 – 3,5]	7 (10)	7 [0 – 14]	9,4 (7,9)	8,5 [3 – 15,5]	3,5 (5)	3,5 [0 – 7]	1,1 (0,4)	1 [1 – 1]
Rheumatic disease	4,3 (3,7)	4,5 [1 – 6]	24,2 (41)	9 [0 – 21]	7 (9)	3 [0 – 11]	42 (48)	30 [15,5 – 62,5]	1,8 (0,8)	2 [1 – 2]
Infectious disease	8,7 (2,5)	9 [7,5 – 10]	11 (16,4)	2 [1,5 – 16]	10,7 (16,7)	1 [1 – 15,5]	4,5 (6,4)	4,5 [0 – 9]	1,7 (0,6)	2 [1,5 – 2]
Drugs - toxics	3,5 (3,5)	3,5 [1 – 6]	21 (12,7)	21 [12 – 30]	-	-	-	-	-	-

Statistical dispersion of mean is expressed with standard deviation (SD). Statistical dispersion of median is expressed in interquartile range [Q1 – Q3].

Table 8. Assistance activity according to cancer types

	Referral – RDU (days)		RDU – Diagnosis (days)		Test request – medical report (days)		Medical report – next visit (days)		Nº of visits (N)	
	Mean	*Median*	*Mean*	*Median*	*Mean*	*Median*	*Mean*	*Median*	*Mean*	*Median*
Pancreatic	2,7 (2,3)	2 [1,5 – 3,5]	8 (14)	1 [0 – 9,5]	8,1 (14,1)	1 [0 – 10]	4 (4,6)	3 [0 – 6]	1,9 (0,7)	2 [1,5 – 2]
Colon	3,6 (2,4)	3 [2 – 5]	22 (42)	1,5 [0 – 44]	10,8 (8)	10 [4 – 15]	4 (2)	4 [3 – 5]	2 (1,2)	2 [1 – 2]
Gastric	2 (0,8)	2 [1,5 – 2,5]	14 (13,9)	7 [6 – 18,5]	14 (13,9)	7 [6 – 18,5]	2 (2,8)	2 [0 – 4]	1,5 (0,6)	1,5 [1 – 2]
Lymphoma	3 (1)	3 [2,5 – 3,5]	26,3 (20,7)	30 [17 – 37,5]	19 (22,6)	8 [6 – 26,5]	-	-	1,3 (0,6)	1 [1 – 1,5]
M1 without primary tumour	1,7 (0,6)	2 [1,5 – 2]	2,7 (3,8)	1 [0,5 – 4]	2,7 (3,8)	1 [0,5 – 4]	-	-	1,3 (0,6)	1 [1 – 1,5]
Prostatic	10 (10,8)	7 [4 – 14,5]	12,7 (8,7)	15 [9 – 17,5]	6 (7,9)	3 [1,5 – 9]			2 (1)	2 [1,5 – 2,5]
Lung	3,3 (0,6)	3 [3 – 3,5]	17 (12,5)	16 [10,5 – 23]	16,3 (12,7)	14 [9,5 – 22]	2 (1,4)	2 [1 – 3]	1,7 (0,6)	2 [1,5 – 2]

Statistical dispersion of mean is expressed with standard deviation (SD). Statistical dispersion of median is expressed in interquartile range [Q1 – Q3].

Table 10. Total number of complementary tests

	Nº of tests	% of all patients
CT[1]		
Abdominal CT	30	34,1
Thoracic CT	5	5,7
Thoracic/Abdominal CT	16	18,2
Other CT (cranial)	4	4,5
Endoscopy		
Gastroscopy	22	25
Colonoscopy	13	14,8
Bronchoscopy	3	3,4
Bone scan	4	4,5
MRI[2]		
MR[3]	3	3,4
MR Cholangiopancreatography	2	2,3
Biopsy		
Lymph node dissection	1	1,1
Hepatic FNA	2	2,3
Liver biopsy	1	1,1
Pleural biopsy	1	1,1
Prostatic biopsy	1	1,1
Temporal artery biopsy	1	1,1
Radiography		
Mammography	1	1,1
Knee radiograph	1	1,1
Wrist radiograph	1	1,1
Echography		
Echocardiogram	3	3,4
Renal/bladder echography	1	1,1
Cytology exam		
Pleural fluid	2	2,3
Pericardial fluid	1	1,1
Peritoneal fluid	1	1,1
Electromyography	1	1,1
Oesophageal manometry	1	1,1
Others		
PPD skin test	1	1,1
Rapid urease test	1	1,1

1. Computed Tomography; 2. Magnetic Resonance Imaging; 3. Magnetic Resonance