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ORIGINAL ARTICLE

Increased post-hospital mortality of polypathological patients during COVID-19 pandemic

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Abstract

Background: The impact of COVID-19 pandemic on post-hospital mortality of polypathological patients is unknown. **Methods**: We compared two cohorts of polypathological patients: patients discharged during the first quarter of the years 2017-2019 (pre-pandemic cohort), and patients discharged in the first quarter of 2020 (pandemic cohort). Demographic characteristics, prognostic PROFUND score, use of hospital services after discharge, and vital status at 1, 3, 6, and 12 months were compared. The influence of the pandemic on 3, 6, and 12-month mortality was analyzed with a multivariant model, including gender, age, and prognostic PROFUND score. **Results**: The pre-pandemic (512 patients) and pandemic (132 patients) cohorts were similar in age (mean 78.8 vs. 79.1-year-old, respectively) and PROFUND prognostic index > 10 (31.9% vs. 37.4%, respectively). There were more men in the prepandemic cohort (59% vs. 49.6%, respectively, p = 0.06). The accumulated 6-month mortality was higher in the pandemic cohort (39.4% vs. 28.7%; p = 0.02), but not at 1, 3, and 12 months. A significant higher risk of accumulated mortality at 6 months in the pandemic cohort remained in multivariant analysis (Odds ratios: 1.63; IC95%: 1.07-2.48). Significant reduction in specialized healthcare utilization during the 12-month period after discharge was found in the pandemic cohort: 42% less emergency visits (p = 0.001), 30% less external office visits (p = 0.023), and 58% less hospitalizations (p = 0.001). **Conclusions**: Risk of 6-month accumulated mortality of polypathological patients discharged around the onset of the COVID-19 pandemic was 63% higher than historic controls. These differences disappeared 12 months after discharge.

Keywords: Polypathological patient. Multimorbidity. Prognosis. Mortality. Internal Medicine. COVID-19.

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Introduction

COVID-19 pandemic has overburdened health-care systems worldwide. There is a great concern about its impact on patients with non-communicable diseases[1]. The care of non-COVID patients has been negatively impacted since the start of the pandemic, particularly during its waves and lock-down periods. It has been reported that the pandemic affected adversely health-care for cancer[2], cardiovascular disease[3], and other conditions[4]. Mortality rates by indirect causes during COVID-19 pandemic are supposed to be very high. In 2020, the excess of mortality in the Americas Region and European Region were, respectively, 60% and 50% higher than that registered by COVID-19[5]. In Spain, the lockdown period was very strict and lasted 14 weeks (from mid-March to June 21, 2020), and negative effects on the management of other diseases have been reported[6-8]. In addition, in 2020, the rates of deaths from cardiovascular, neoplastic, and respiratory disorders have increased outside of hospitals by up to 18%, 33.8%, and 8.9%, respectively[9].

There is plenty of information confirming that multimorbidity increases the severity and mortality of COVID-19[10]. However, there is no information regarding the impact of the pandemic on the care and prognosis of patients with complex multimorbidity.

To the best of our knowledge, no information has been published about the impact of pandemic on polypathological patients. This impact should be measured considering other factors that may influence it.

In our hospital, the first hospital admission of a patient with COVID-19 was on February 28, 2020. Soon the hospital reorganized to confront de pandemic. Scheduled and urgent hospital admissions for non-COVID conditions diminished and many outpatient visits were reduced or cancelled. Consequently, follow-up of patients after discharge was also affected. Patients with multiple chronic diseases are very vulnerable during the post-hospital period. We considered it relevant to conduct a study with the objective of determining the impact of the pandemic's onset on the prognosis of newly discharged polypathological patients.

Materials and methods

Costa del Sol Hospital is a 400-bed general hospital located in Marbella (South of Spain). It provides specialized healthcare to a population of 478.150 inhabitants. Between February 28, and December 31, 2020, 482 patients with COVID-19 were admitted to hospital.

Table 1. Functional definition of polypathological patient: The patient who suffers chronic diseases included in two or more of the following clinical categories

Category A A.1: Chronic heart failure with past/present stage II dyspnea of NYHA* A.2: Coronary heart disease
Category B B.1: Vasculitides and/or systemic autoimmune diseases B.2: Chronic renal disease (creatininaemia N 1.4/1.3 mg/dL in men/women or proteinuria†, during ≥ 3 months
Category C Chronic lung disease with past/present stage 2 dyspnea of MRC† or FEV1 < 65% or basal SatO2 ≤ 90%
Category D D.1: Chronic inflammatory bowel disease D.2: Chronic liver disease with evidence of portal hypertension§
Category E E.1: Stroke E.2: Neurological disease with permanent motor deficit, leading to severe impairment of basic activities of daily living (Barthel index < 60) E.3: Neurological disease with permanent moderate-severe cognitive impairment (Pfeiffer's test with ≥ 5 errors)
Category F F.1: Symptomatic peripheral artery disease F.2: Diabetes mellitus with proliferate retinopathy or symptomatic neuropathy
Category G G.1: Chronic anemia (Hb < 10 g/dL during ≥ 3 months) due to digestive-tract losses or acquired hemopathy not tributary of treatment with curative intention G.2: Solid-organ or hematological active neoplasia not tributary of treatment with curative intention
Category H H.1: Chronic osteoarticular disease, leading to severe impairment (limitation of the patient's ability to transfer alone safely from bed to chair or wheelchair) H.2: Having suffered an osteoporotic hip fracture

*Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnea.
†Albumin/creatinine index N300 mg/g, microalbuminuria N3 mg/dL in urine, albumin N300 mg/day in 24-h urine, or albuminuria/min N200 µg/min.
‡Short of breath when hurrying or walking up a slight hill.
§Presence of clinical, analytical, echographic or endoscopic data of portal hypertension.
Hb: hemoglobin; NYHA: New York heart association;
MRC: medical research council; FEV1: forced expiratory volume in the 1 s.
With permission from Bernabeu-Wittel et al.[12]

Polypathological patients are frequently admitted to the Internal Medicine department, representing more than one third of its admissions in 2019. Polypathology definition requires the presence of two or more symptomatic chronic diseases (from a pre-defined list of chronic conditions associated to frequent exacerbations and a negative impact on functional status and frequent use of health-care services, Table 1)[11,12]. It has been shown

Table 2. Profund index score

Variable	Points
Age ≥ 85 (years)	3
Active neoplasia	6
Dementia	3
III-IV NYHA dyspnea or 3-4 mMRC	3
Delirium during last hospital admission	3
Hb < 10 g/dL	3
Barthel index < 60	4
Absence of caregiver or caregiver is other than spouse	2
≥ 4 hospital admissions over the last 12 months	3

Low-risk: 0-2 points; low-intermediate risk: 3-6 points; intermediate-high risk; 7-10 points; high risk: 11 or more points. Hb: hemoglobin; NYHA: New York heart association; MRC: medical research council.
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that 1.38% of the population and 30-38% of patients admitted to Internal Medicine departments fulfill these criteria[11]. PROFUND index is growingly employed in many internal medicine departments in Spain to establish the prognosis in "polypathological patient"[13] (Table 2). It stratifies the 12-month mortality risk into four groups and has been validated in other cohorts, with accuracy also to predict 4-year mortality[14]. The reported mortality rate within 1 year for patients who obtain a score > 10 varies from 61.3% to 68%[13].

The present study compared two cohorts of polypathological patients discharged from the internal medicine department. The "pre-pandemic" cohort was composed by patients discharged during the first quarter of years 2017-2019. The "pandemic" cohort included those patients released during the first quarter of 2020. Characteristics of patients on hospital discharge were registered: age, gender, and dichotomized PROFUND index (PI) (≤ 10 vs. > 10). Vital status at 1, 3, 6, and 12 months and use of hospital services (visits to emergency or outpatient non-surgical specialties, and hospitalization) in the first 12 months after discharge were retrieved. We compared the values of these variables in both groups.

PROFUND index score and demographic data were obtained from a prospectively registered database of polypathological patients in our department. Information on hospital resources was gathered using the HP-HCIS electronic record program. The National Death Registry was used to track down deaths that took place outside of hospitals after discharge.

For descriptive analysis, central tendency and dispersion measures were calculated for quantitative variables, and frequency distribution for qualitative variables. Bivariate analysis was performed for comparison of both cohorts, employing ji-square test for qualitative variables and Student t-test for quantitative variables. Survival probability at 1-year was represented using Kaplan-Meier method, and comparison of the survival curves of both cohorts was performed with Log Rank test.

The influence of belonging to the pandemic cohort on accumulated mortality at 3, 6, and 12 months, was analyzed with a logistic regression model, adjusting by age, gender, and dichotomized PROFUND index (≤ 10 vs. > 10). Backward method stepwise (Wald) was employed and the independent study variables had an entry criterium of p = 0.05 and exit criterium of p = 0.1. Odds ratios (OR) and their corresponding 95% confidence intervals were calculated (CI 95%); goodness of fit was evaluated with Hosmer–Lemeshow test, and variance with Nagelkerke's square R.

In the different analysis, statistic significance was established when p < 0.05. For statistics calculation, SPSS v.28 was employed.

Results

The pre-pandemic cohort was composed of the 512 polypathological patients discharged during the first quarters of the years 2017-2019, while the pandemic cohort included the 132 polypathological patients discharged during the first quarter of 2020. Both cohorts were comparable in terms of age (78.8 year-old in prepandemic vs. 79.1-in pandemic), sex (50.4% vs. 49.6% women, respectively), and median hospital stay (7 vs. 8 days, respectively). The diagnostic categories that defined polypathology remained similar between patients in the prepandemic and pandemic periods, except for categories F and H which were more prevalent in the prepandemic cohorts, although with a small number of patients (Fig. 1). Category F comprises patients with symptomatic peripheral artery disease, diabetes mellitus with proliferative retinopathy, or symptomatic neuropathy, while category H pertains to those with chronic osteoarticular disease that significantly impairs basic activities of daily living.

The pandemic cohort had a slightly higher mean value of the profund index and an increased prevalence of patients with a poorer prognosis (Profund index > 10) when compared to the non-pandemic cohort. However, the observed difference was not found to be statistically significant (Table 3).

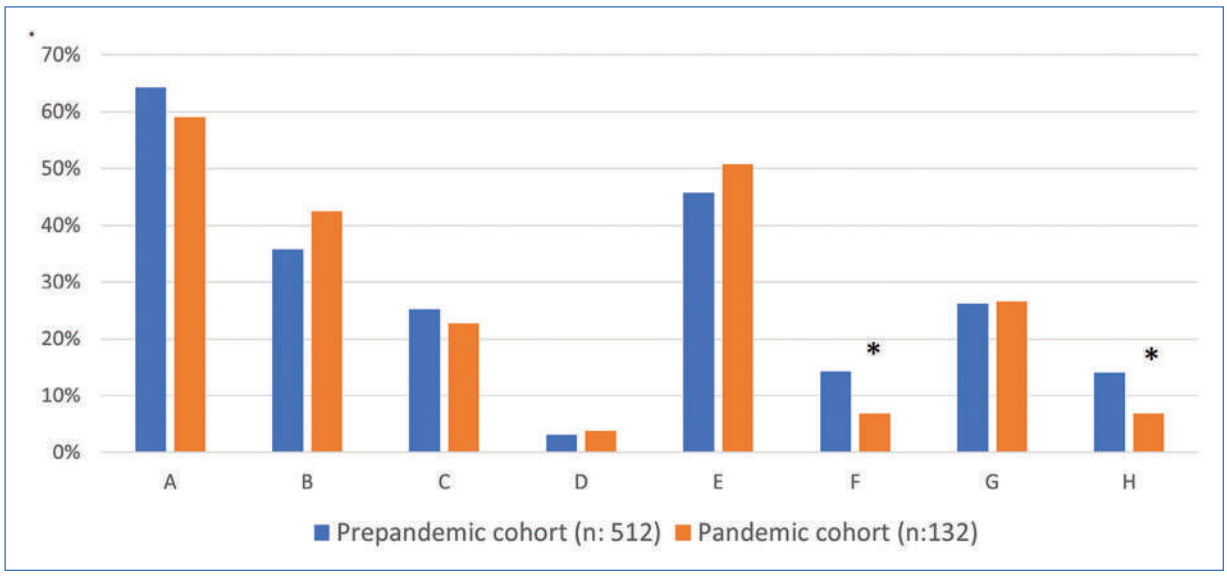


Figure 1. Diagnostic categories of polypathology in prepandemic and pandemic cohorts.
*p < 0.05.

The results showed that the mortality rates were higher in the pandemic cohort at 1, 3, 6, and 12-months. However, the difference between the two groups was only statistically significant at 6 months (39.4% vs. 28.7%; p = 0.02), and although the difference was present at 12 months, it did not reach statistical significance (44.7% vs. 37.1%; p = 0.13) (Table 3). Only one out of the 59 patients who died during the first 12-months after discharge had COVID-19 as the cause of death. The proportion of patients who died in the hospital during the first 12 months was similar in both cohorts: 30% (57 patients) in the prepandemic versus 33.9% (20 patients) in the pandemic cohort (p = 0.63).

Adjusted mean 1-year accumulated survival was 8.8 months (IC95%: 8.3-9.2) in the pre-pandemic cohort, versus 7.8 months (IC95%: 6.9-8.7) in the pandemic cohort (p = 0.101) (Fig. 2).

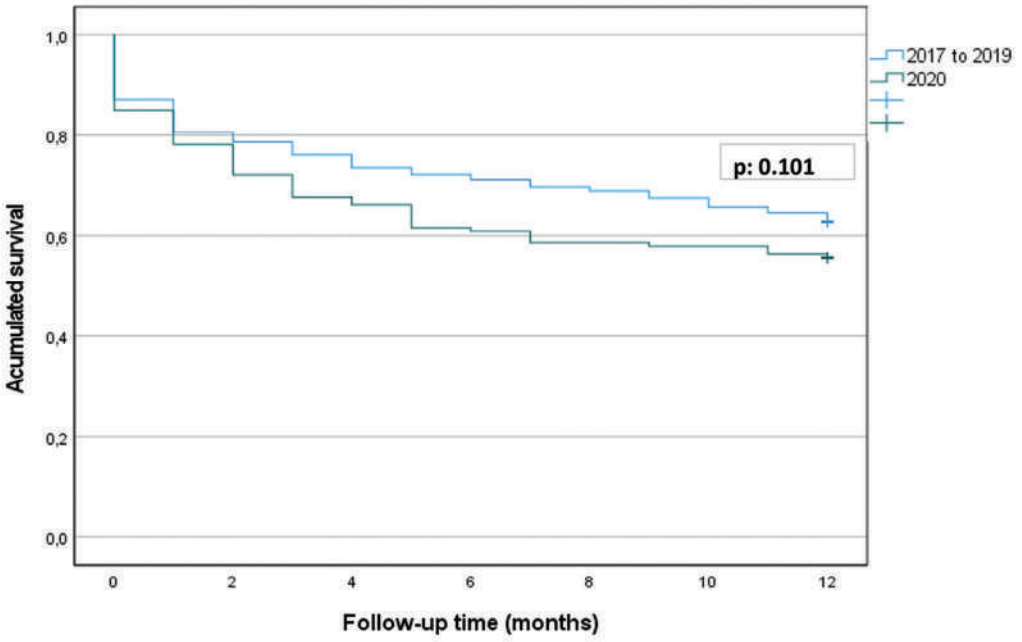
The multivariant analysis with accumulated mortality at 3, 6, and 12 months as a result variable, adjusted by the four evaluated variables, showed that belonging to the pandemic cohort was associated to a higher mortality only at 6 months (OR 1.63, 95% CI 1.07-2.48) (Table 4). Goodness of fit of the logistic regression models of accumulated mortality at 3, 6, and 12 months after hospital discharge was 0.435, 0.598, and 0.737, respectively, and variances (Nagelkerke's square R) were similar (0.111, 0.105, and 0.111, respectively).

Mean accumulated use of specialized health-care resources during the 1-year after discharge was lower in the pandemic cohort in comparison with the prepandemic cohort: 42% fewer emergency visits (p = 0.001), 30% fewer external non-surgical consultation (p = 0.023), and 58% fewer hospitalizations (p = 0.001) (Fig. 3). During the same time period, total hospital activity decreased less than that reported in polypathological patients in the emergency department and hospitalization (25% fewer emergency visits and 11.8% fewer hospital admissions), and outpatient activity decreased similarly (34.4% fewer visits).

Table 3. Characteristics at hospital discharge of the two study cohorts and accumulated post-hospital mortality

Variables	Prepandemic cohort (n = 512)	Pandemic cohort (n = 132)	P
Male gender†	298 (59.0)	65 (49.6)	0.066
Age*‡	78.8 (11.0)	79.1 (11.6)	0.763
PROFUND index*	8.23 (5.4)	9.41 (5.9)	0.647
PROFUND index > 10	159 (31.9)	49 (37.4)	0.28
Post-hospital mortality (months)			
1	98 (19.1)	29 (22.0)	0.545
3	122 (23.8)	43 (32.6)	0.052
6	147 (28.7)	52 (39.4)	0.024
12	190 (37.1)	59 (44.7)	0.135

Data are presented as n (%) or *mean (SD).
†9 missing values in prepandemic and 1 in pandemic cohort.
‡1 missing value.
SD: standard deviation.



number of patients at risk

Month	0	2	4	6	8	10	12
Prepandemic cohort	511	412	389	369	356	345	330
Pandemic cohort	133	104	90	82	78	77	75

Figure 2. Accumulated 12-month survival in the two study cohorts.

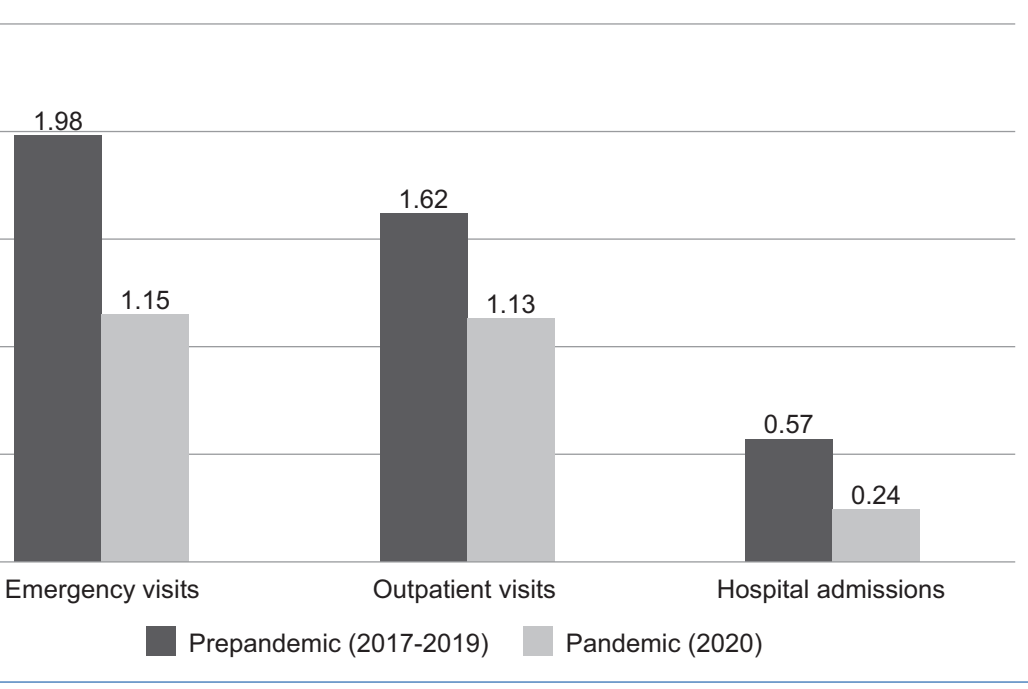


Figure 3. 1-year-adjusted mean number of accumulated emergency visits, outpatient visits, and hospital admissions in each cohort.
*$p < 0.05$

Table 4. Logistic regression models of accumulated mortality at 3, 6, and 12 months after hospital discharge

Accumulated mortality (months)	Variables	β	P	OR	CI 95%
3	Pandemic cohort	0.44	0.053	1.55	0.99-2.40
	Male gender	0.34	0.087	1.41	0.95-2.08
	Age (years)	0.33	0.003	1.03	1.01-1.06
	PROFUND index > 10	0.96	< 0.001	2.62	1.76-3.89
6	Pandemic cohort	0.49	0.023	1.63	1.07-2.48
	Male gender	0.38	0.042	1.47	1.01-2.13
	Age (years)	0.02	0.014	1.02	1.01-1.04
	PROFUND index > 10	0.98	< 0.001	2.65	1.82-3.87
12	Pandemic cohort	0.33	0.116	1.39	0.92-2.09
	Male gender	0.50	0.006	1.64	1.15-2.34
	Age (years)	0.03	0.001	1.03	1.01-1.05
	PROFUND index > 10	0.90	< 0.001	2.46	1.71-3.55

CI: confidence interval; OR: odds ratio.

Discussion

This study showed that polypathological patients who were discharged during the COVID-19 surge had a 63% higher mortality rate after 6 months compared to historical controls from the previous 3 years. This result highlights the influence of the pandemic on this susceptible patient population and may suggest that patients with multiple health conditions are more vulnerable to a decrease in health-care quality. Notably, this increased mortality persisted even after accounting for age differences, sex, and PROFUND prognostic index. Although accumulated mortality was also higher in those patients at 12 months, it did not reach statistical significance. The use of specialized healthcare during the 12-month follow-up was strikingly reduced.

The COVID-19 pandemic has shown to increase mortality and morbidity in some acute non-COVID medical and surgical conditions[15,16]. Multiple studies indicate that non-COVID conditions have suffered a negative impact by the pandemic: increased in-hospital mortality[17] decrease cancer screening and diagnosis[18], and increased cardiovascular mortality[19], among others.

Routine health-care deterioration for chronic diseases has been generalized[20]. Mortality from cardiovascular illnesses and the central nervous system raised to 2.8% and 5.3% in Spain in 2020, respectively, suggesting an impact of pandemic on elderly chronic patients[9]. To the best of our knowledge, there is no published information regarding the post-hospital mortality of chronic patients during the early pandemic period. One-third of admissions to internal medicine departments are polypathological patients[11]. Despite the fact that these patients represent a hight proportion of hospital admissions, there is a dearth of data on their survival in the early months after discharge during the initial stages of the COVID-19 pandemic. This information gap highlights the need for further research on this vulnerable patient population in the context of the pandemic.

In Spain in 2020, there was an increase in mortality compared to 2019 in nursing homes (33.7%), households (25.7%), and hospitals (15.6%). The increase in mortality at home was primarily due to neoplasms, diseases of the circulatory system, and respiratory diseases (with increases of 33.8%, 18%, and 8.9%, respectively, compared to the previous year)[9]. Most of the patients in our study died outside the hospital, where the population mortality increase was higher during the pandemic period. This increase in out-of-hospital mortality during lockdown has been reported in other countries as well. A study conducted in Italy reported a 43.2% increase in out-of-hospital mortality during the initial lockdown period, with increases in deaths related to neoplasms (76.7%), endocrine and metabolic disorders (79.5%), and cardiovascular diseases (32.7%). These findings suggest that the pandemic and its associated restrictions may have had a significant impact on mortality rates for various causes

outside of hospitals[21]. The reported increase in non-COVID mortality rates in some countries has been shown to disproportionately affect disadvantaged minorities, which have a higher prevalence of chronic diseases. A study conducted in the USA reported that these minorities accounted for 36% of COVID-19 deaths and 70% of excess non-COVID deaths[22].

Our study has several strengths. First, our group has extensive experience in the management of polypathological patients, who represent more than one-third of hospitalizations in our internal medicine department. Second, the risk stratification tool, PROFUND index, is routinely employed in the past 5 years in our department, and we have validated its value to predict both early and late mortality[23]. The 12-month mortality rate of the prepandemic cohort (37.1%) in our study is quite like the 38% reported by a recent series[24]. Third, although specific causes of death were not analyzed, only one out of our 59 patients died by COVID-19 infection, which eliminated its influence on mortality.

Some limitations of the present study should be mentioned. First, the pandemic's influence on health-care provision has changed with time, with the largest effects occurring during the first several months of the outbreak. This could account for the considerable impact on accumulated mortality at 6 months, as well as the decrease of this effect in the posterior months as health-care service became more normalized. Furthermore, while the PROFUND prognostic index was used to adapt the predicted model for mortality, clinical factors not evaluated in this index may have influenced death.

The fact that we only found statistical significance in mortality post-discharge at 6 months in our study may be related to the greater impact on the health-care system during the initial phase of the pandemic and reduced patient access to care due to confinement. The increase in mortality observed in the Spanish population during 2020 was most pronounced in March and April of that year, with nursing homes, households, and hospitals reporting an increase of 201.4%, 52.1%, and 50.6%, respectively[9].

Larger studies with more predicting factors are needed, however, to determine the impact of the pandemic on these comorbid, complex, and polypathological individuals, particularly during stringent lockdown settings.

Conclusions

Polypathological patients who were released from the hospital during the initial stage of the COVID-19 pandemic had a mortality rate 63% higher after 6 months compared to the same period of the preceding 3 years. However, this mortality difference was not observed after 12 months. In addition, there was a marked reduction in the utilization of hospital services during the 12-month following the hospital discharge.

Funding

None.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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ORIGINAL ARTICLE

Searching differences in patients with heart failure with clinical suspicion of cardiac amyloidosis: the REGAMIC study design

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Abstract

Introduction and objectives: Cardiac amyloidosis (CA) is not a rare cause of heart failure (HF). In Spain, more than 60% of HF patients admitted to hospitals are treated in Internal Medicine Services. REGAMIC is a registry designed by the HF Working Group of the Spanish Society of Internal Medicine to improve the suspicion criteria and the selection of patients in whom CA must be ruled out. The main objective is to evaluate the differential characteristics between two groups of HF patients with suspicion of CA: confirmed vs ruled out cases. The secondary objectives are to evaluate the data on which investigators have based the suspicion of CA, and to identify prognostic differences between both groups. **Methods:** A multicenter, observational, prospective, cohort study of at least 600 patients, with a 2-year follow-up. Inclusion criteria: patients of Internal Medicine Services, aged ≥ 18 years, with HF and left ventricular hypertrophy (septum or posterior wall ≥ 12 mm), with suspicion of CA. Clinical, electrocardiographic, echocardiographic, and follow-up data will be compared between both groups of patients. **Results and discussion:** If the recommendations of the 2021 European Society of Cardiology Consensus on CA are followed, a large number of patients should be studied to rule out CA. REGAMIC can improve the selection of patients in whom CA will be ruled out and make the study more cost-effective. **Conclusions**: Our registry aims to improve the knowledge about differential characteristics between HF patients with clinical suspicion of CA and may increase knowledge of the natural history of the disease.

Keywords: Cardiac amyloidosis. Heart failure. Multicenter registry. Internal medicine.

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Introduction

Different studies on the prevalence of cardiac amyloidosis (CA) as a cause of heart failure (HF) have shown that it is not a rare disease, its prevalence varying between 4 and 20% depending on the groups of patients studied[1-10]. Various types of amyloid can infiltrate cardiac tissue, but 98% of CA cases are secondary to transthyretin amyloidosis (ATTR), in wild-type (ATTRwt) and hereditary (ATTRv) varieties, or primary amyloidosis (AL)[11-13]. However, ATTR cardiomyopathy (ATTR-CM) is an underdiagnosed entity because it requires a high index of suspicion, and early diagnosis is of great importance to offer patients the most appropriate therapy[14]. For this reason, the European Society of Cardiology (ESC) has published a consensus that addresses the clinical scenarios to suspect CA and proposes a diagnostic algorithm to aid diagnosis[15]. One of these scenarios has caused some controversy among internists and other medical specialists, since it requires ruling out CA in all HF patients, aged ≥ 65 years and with a left ventricle wall thickness ≥ 12 mm, a very frequent patient profile among patients with HF which implies a high consumption of healthcare resources.

In Spain, 60% of HF patients who are admitted to hospitals are cared for in Internal Medicine Services[16-18], and a study conducted by the HF and Atrial Fibrillation Working Group of the Spanish Society of Internal Medicine (the PREVAMIC study)[19,20] has estimated the prevalence of different types of CA in HF patients attended by internists at 20.1%.

Now, this same working group has considered useful to carry out a multicenter registry (REGAMIC) in internal medicine units to evaluate differential characteristics between HF patients in whom the presence of CA is suspected. The patients will be collected regardless of whether the diagnosis of CA is confirmed or not, which will improve the criteria for suspicion of this disease.

Objectives

The main objective of this registry is to evaluate the differential characteristics between two groups of HF patients in whom there is a clinical suspicion of CA:
- Group 1: patients in whom CA is confirmed.
- Group 2: patients in whom CA is ruled out.

Clinical characteristics, analytical, electrocardiographic, echocardiographic, and follow-up data in both groups will be compared.

Secondary objectives:
- Evaluate the clinical data and complementary tests on which investigators have based their suspicion of CA.
- Identify prognostic differences between both groups by comparing the rates of readmissions, mortality, and other events of patients with CA and without CA over a 2-year period to improve understanding of the natural history of the disease.

Methods

Design and study population

This is a multicenter, observational, prospective cohort registry with a 2-year follow-up, with recruitment beginning in January 2022. It is also possible to retrospectively include patients who met the registry criteria during the year 2021 and were studied to rule out CA; the follow-up at 24 months of these patients can be done in all of them from January 2023.

HF patients attended by internal medicine specialists who meet the inclusion criteria of the registry and in whom the investigator suspects CA (types ATTRv, ATTRwt or AL) and have been studied to confirm or rule out CA will be included.

Patient selection and inclusion/exclusion criteria

Eligibility requirements included inpatients or outpatients from the Internal Medicine departments, an age of at least 18 years, and any ejection fraction. Only patients who meet the diagnostic criteria for HF of the Guidelines of ESC of 2021[21], with left ventricular hypertrophy (LVH) (septum or posterior wall ≥ 12 mm), and a well-founded clinical suspicion of CA, according to the recommendation published by the ESC Working Group on Myocardial and Pericardial Diseases in 2021[15], will be included. Furthermore, patients were required to have an elevated plasma level of N-Terminal Pro-Brain Natriuretic Peptide (NT-proBNP)[22]. The inclusion and exclusion criteria are detailed in table 1.

Patients who do not accept to participate in the registry will be excluded.

Study variables and data collection

The study consists of an inclusion visit during a hospital admission or in outpatient clinic. Follow-up will be for 2 years, with review in outpatient clinics or by telephone. The study variables that will be collected at each visit are detailed in table 2. Data will be included in an electronic medical record accessed with a personal password. To preserve confidentiality, no personal data will be stored.

Table 1. Inclusion and exclusion criteria

Inclusion criteria
– Age ≥ 18 years. Both genders – Inpatients or outpatients from the Internal Medicine Departments – Heart failure criteria according to the 2021 ESC European Guidelines[21] – Echocardiogram performed in the previous 24 months or at time of inclusion – Left Ventricular Ejection Fraction: any value – NT-proBNP > 1800 or BNP > 400 in AHF, or NT-proBNP > 400 or BNP > 100 in a stable situation (pg/ml)[22] – Well-founded clinical suspicion that the patient may be suffering from Cardiac Amyloidosis (ATTRv, ATTRwt or AL) based on the presence of red-flags for this pathology, according to the recommendation published by the ESC Working Group on Myocardial and Pericardial Diseases in 2021[15]: • Ventricular hypertrophy ≥ 12 mm and one or more of the following criteria: ■ Heart failure in ≥ 65 years ■ Aortic stenosis in ≥ 65 years ■ Hypotension or Normotensive if previously hypertensive ■ Sensory involvement, autonomic dysfunction ■ Peripheral polyneuropathy ■ Proteinuria ■ Skin bruising (eg, periorbital purpura) ■ Bilateral carpal tunnel syndrome ■ Ruptured biceps tendon ■ In CMR: Subendocardial / transmural late gadolinium enhancement (LGE), or increased extracellular volume (ECV) ■ In ECO: Reduced longitudinal strain with apical sparing ■ Reduced QRS voltage to mass ratio ■ Pseudo Q waves on ECG ■ Atrioventricular conduction disease ■ Possible family history of ATTRv
Exclusion criteria
– Patients who refuse to participate

BNP: brain natriuretic peptide; NT-proBNP: N-Terminal Pro-Brain Natriuretic Peptide.

Sample size

We estimate a sample size of at least 150 patients in the Group with CA confirmed, and a total of at least 600 patients.

Statistical analysis

The continuous variables will be expressed as the value of the mean and standard deviation or as median and interquartile range, depending on the normality of their distribution. The categorical variables will be expressed as percentages or rates. A descriptive analysis of the data will be carried out, and a comparative analysis in relation to variables that are of interest for the objectives of the study.

The comparison will be made using the Chi-square test for categorical variables and Student's t-test for normal quantitative variables. For non-normal quantitative variables, the non-parametric U-Mann Whitney test will be used. Regarding the follow-up data, the association of different variables with readmission and mortality data will be assessed using the univariate and multivariate analysis. An analysis of survival curves will also be performed using the Kaplan–Meier method using the log-rank test. Statistical significance will be considered a $p < 0.05$. The analysis will be carried out with the statistical package IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.

Ethical aspects

The patients included will be treated following the medical care according to art, since being a registry it does not modify the usual clinical practice. The study will be carried out in agreement with the Declaration of Helsinki and according to Spanish Organic Law 3/2018, of December 5, on the Protection of Personal Data and Guarantee of Digital Rights. An informed consent will be obtained from all participating subjects.

This study has been approved by the Clinical Research Ethics Committee of the Virgen Macarena and Virgen del Rocío University Hospitals of Seville (Spain); and is registered on the website ClinicalTrials.gov with the number NCT05176548.

Table 2. Study variables at inclusion and follow-up visits

Inclusion visit	
Demographic/general variables	Age Gender Social and family situation
HF-related variables	HF aetiology and year of first HF diagnosis NYHA scale Previous admissions for AHF Previous ED visits for AHF HF self-control education
Comorbidities	Relevant previous diseases Charlson Comorbidity Index
Functional and cognitive status	Barthel Index Pfeiffer test Frail scale
Relevant data specific to Amyloidosis	Presence of "red-flags" of Amyloidosis
Symptoms, signs and clinical examination findings	Related to HF or Amyloidosis
Laboratory parameters	Blood cell count Biochemical parameters* Natriuretic peptides Cardiac Troponin Carbohydrate antigen 125 Serum free light chain, serum and urine protein electrophoresis with immunofixation
Complementary procedures	Electrocardiogram Transthoracic Echocardiogram Cardiac scintigraphy (^{99m}Tc-DPD/PYP/HMDP) Cardiac MR (if performed) Biopsies (if performed)
Management	Drugs: baseline treatment Drugs: treatment after Amyloidosis diagnosis Non-pharmacologic treatments
Genetic study	TTR gene mutations
Final diagnostic	Amyloidosis: Yes or Not Type of Amyloidosis
Two-year follow-up visit	
Outcomes	Follow-up events Vital status and causes of death Admissions for HF and other causes ED visits for HF and other causes

AHF: acute heart failure; ED: emergency departments; HF: heart failure; MR: magnetic resonance; NYHA: New York Heart Association; ^{99m}Tc-DPD/PYP/HMDP: ^{99m}Technetium- 3,3-diphosphono-1,2-propanodicarboxylic acid / pyrophosphate / hydroxymethylene diphosphonate; TTR: transthyretin.
*Including glucose, urea, creatinine, sodium, potassium, total proteins, bilirubin and liver enzymes.

Discussion

According to the data from the National Institute of Statistics, in Spain in 2021 there were 64,044 admissions for HF, of which 90% were ≥ 65 years of age, and more than 60% of these patients are cared for in internal medicine departments[23]. This implies that more than 35,000 patients with HF and aged ≥ 65 years are admitted annually to internal medicine services. In addition, data from the Spanish HF registry (RICA)[24] have clarified that more than 50% of these patients have LVH ventricular ≥ 12 mm.

If the recommendations of the ESC Consensus on CA are followed, which indicate that CA should be ruled out in all HF patients, aged ≥ 65 years, and LVH ≥ 12 mm[15], a large number of patients (≈ 18,200) should be studied to rule out CA. It supposes that more than 50% of hospitalized patients with HF would be eligible for a study to find out if they have CA. This has generated controversy

among internists, since it requires a high consumption of healthcare resources. Also, to this high number, we should add the outpatients with these characteristics and patients cared by cardiologists or other specialists.

Only the consensus of the German Cardiac Society[25] establishes similar criteria to those of the ESC, and recommends ruling out CA in patients with LVH ≥ 12 mm-in the absence of hypertensive heart disease-, age > 60 years, symptoms of HF and still normal-sized ventricles.

Other documents, such as those published by Maurer et al.[26] by the American College of Cardiology[27], by the Canadian Cardiovascular Society/Canadian HF Society[28], and by the Japanese Circulation Society[29] basically recommends suspecting CA in the presence of clinical features (clues or "red flags") that are associated with CA, without specifying scenarios such as the one described in the ESC consensus. Rapezzi et al. have published a comparative study of the different documents on CA showing the differences in the criteria for a diagnostic evaluation for CA of the different scientific societies[30].

In addition, Internal Medicine patients with HF compared to those attended by Cardiology are older, more frequently women and with a greater number of associated comorbidities and preserved LVEF[31], and the cost-effectiveness of performing CA diagnostic tests in this type of patient is unknown.

Some retrospective studies have been carried out to improve the suspicion of CA describing characteristics of contemporary pathways leading to ATTRwt-CA diagnosis (Tini et al.[32]); or the model developed by Suh et al.[33] which provided an efficient means for identifying HF patients who are more likely to have ATTR-CM. Davies et al.[34] make another proposal with 6 clinical variables that may be useful to guide use of PYP and increase recognition of ATTR-CM among HF patients with preserved ejection fraction. Caponetti et al.[35] proposed a screening algorithm for patients belonging to high-risk clinical settings for CA: ECG, echocardiogram and cardiac biomarkers can all be used as a first step method in the suspicion of CA, although echocardiogram is imperative before starting a diagnostic work-up; and they suggest that a multimodality approach and new developed techniques such positron emission tomography fluorine tracers or artificial intelligence may contribute to strike up extensive screening programs for an early recognition of the disease. But we believe that studies with a prospective design are necessary to provide new data that allow better selection of patients in whom diagnostic studies to rule out CA are cost-effective.

For this reason, we consider it useful to carry out this prospective registry, which can contribute to improving knowledge about the differences between patients in whom CA is suspected, in addition to assessing the criteria used by internists in these patients to suspect CA.

Strengths and weaknesses

The main strength of this registry is that it is multicenter and prospective, and that it includes all patients in whom CA is suspected, regardless of whether the diagnosis of CA is confirmed or not. Another strength is the long-term follow-up of patients (24 months) that will provide data on the natural history of the disease.

The main limitation is that it is carried out only with Internal Medicine patients and the data may not be extrapolated to other patients. It is possible that the type of CA is not achieved in all patients, especially if it requires invasive tests, due to the advanced age and comorbidity of these patients. And we also have to consider that applying the ESC criteria, a large number of patients should be studied to rule out CA and this requires a high consumption of health resources.

Conclusions

CA is a frequent and underdiagnosed pathology in people over 65 years of. High suspicion is required for diagnosis. There are few prospective works that study differences in patients with suspected CA. This registry will contribute to improve knowledge of this pathology in the Internal Medicine setting, and could provide data that improves the cost-effectiveness of the CA study.

Key points

What is known about the topic?

- CA is a not rare cause of HF.
- In Spain, 60% of HF patients admitted to hospitals are cared for in Internal Medicine Services.
- The European Society of Cardiology (ESC) has published a consensus that proposes ruling out CA in all HF patients, aged ≥ 65 years and with a left ventricle wall thickness ≥ 12 mm, a very frequent patient profile among internal medicine patients with HF.

What does this study add?

- The REGAMIC registry can improve knowledge of the differences between patients in whom CA is suspected, confirmed versus ruled out.
- It can contribute to understanding the criteria used by internists to suspect CA.
- Also this study can provide new data that allow a better selection of HF patients in whom diagnostic studies to rule out CA are cost-effective.

– On the other hand, it can increase knowledge of the natural history of the disease.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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REVIEW ARTICLE

Evidence of the usefulness of VEXUS score in the diagnosis and treatment of the syndrome cardiorenal: a narrative review

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Abstract

Cardiorenal syndrome (CRS) includes a spectrum of disorders affecting both the heart and the kidneys in which acute or chronic dysfunction in one organ leads to acute or chronic dysfunction in the other. The use of Point-of-Care ultrasound (POCUS) and specifically the VExUS score seems to play an important role in the detection of venous congestion, being a useful tool to complement the physical examination of the patient, allowing the establishment of a targeted therapeutic approach. CRS is a entity that presents a challenge for the clinician, from the difficulty in establishing the etiology to the need to monitoring and follow-up of the chosen treatment. Point-of-Care ultrasound and specifically the VExUS Score emerged promisingly for the evaluation of patients with kidney injury and congestion. In this context, it makes sense to find the evidence that can guide us towards the integrated use of VExUs in such a complex pathology and common as CRS. A article review was made for systematic reviews, meta-analyses, observational studies, original studies, articles on evidence-based medicine sites published in the last 10 years, in English and Spanish. 43 results were obtained, of which 13 met the inclusion criteria. In conclusion, most of the studies carried out correspond to post-surgical patients, and despite the fact that VExUS is increasingly present in the literature, it is necessary to generate evidence to know if it could be useful to manage, assess and adjust the treatment of our main cohort of patients.

Keywords: Point-of-Care ultrasound. Acute heart failure. Inferior vena cava. Venous excess ultrasound score. Cardio-Renal syndrome. Acute kidney injury.

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Introduction

Cardiorenal syndrome (CRS) encompasses a spectrum of disorders affecting both the heart and kidneys in which or chronic dysfunction in one organ can lead to acute or chronic dysfunction in the other organ. It represents the confluence of heart–kidney interactions through various interfaces[1]. The interdependent relationship between the kidney and the heart was already described as early as 1836 by Robert Bright, who observed significant cardiac structural changes in patients with advanced kidney disease[2].

In 2004 the National Heart, Lung, and Blood Institute established that cardiorenal dysregulation leads to CRS, in which therapy to alleviate the congestive symptoms of HF may be limited by further decline in renal function[3].

CRS can be subdivided into five types to allow characterization by the organ of onset and acuity or chronicity[4]: types 1 and 3 describe acute onset and types 2 and 4 describe chronic onset. CRS type 5 is characterized by simultaneous damage or dysfunction of the heart and kidney due to acute or chronic systemic disorders, such as sepsis or amyloidosis[5]. Although this subdivision helps facilitate diagnosis and treatment, syndrome types can coexist and an acute condition can progress to chronicity if not identified and managed early.

In clinical practice, identifying the initial injury and subsequent events that result in decompensated acute or chronic cardiorenal or renocardiac syndrome can be challenging.

Up to 40% of patients hospitalized for acute heart failure (AHF) have an CRS type 1 (CRS1) phenotype[6], in this type, it was assumed that acute kidney injury (AKI) was associated with a mechanism of damage related to hypoperfusion (for an antegrade mechanism). However, in more than 60% of patients with AHF have congestion without hypoperfusion[7], in this context, congestive nephropathy is a potentially reversible associated with declining renal venous outflow and progressively increasing renal interstitial pressure. Adequately diagnosing congestion continues to be a clinical challenge, venous congestion can lead to a vicious cycle of hormonal activation, increased intra-abdominal pressure, excessive sodium reabsorption in the renal tubules, and volume overload, leading to increased right ventricular stress. Effective decongestion could preserve or even improve renal function[8].

The sensitivity of classic symptoms and signs (dyspnea, ortopneia, jugular venous distention, edema, and rales) is limited[9,10]; the use of complementary diagnostic tests such as radiography and biomarkers such as natriuretic peptic tests or carbohydrate antigen 125 present limitations for the correct identification of venous congestion[11].

We know that congestion confers longer hospital admission time and a higher readmission rate[12,13], as it is related to increased mortality, target organ damage, and an increased incidence of AKI. AKI is an independent predictor of mortality in critical patients and mortality attributable to AKI is 20%.

The splanchnic veins contain between 20% and 50% of the total volume of blood[14]. High intra-abdominal pressure compresses intra-abdominal and intrathoracic blood vessels, compromising microvascular blood flow[15]. Decreased venous drainage results in renal, intestinal and mesenteric venous congestion, edema, and ischemia[16]. Being able to assess the degree of this abdominal and renal congestion could be essential for the management of AHF and CRS.

The use of point-of-care ultrasound (POCUS) plays an important role in the detection of venous congestion, being a useful tool to complement the physical examination of the patient, allowing the establishment of a targeted therapeutic approach[17].

We are familiar with ultrasound markers such as the measurement of the inferior vena cava (IVC) as a marker of central venous pressure, although we can find a dilated vena cava without congestion. More than 20 years ago, in the 1990s, ultrasound markers were described to assess flow changes in the portal vein using pulsed Doppler (PD)[18], more recently a protocol was developed for the measurement of venous congestion. using POCUS, called Venous Excess Ultrasound Grading System (VExUS), which allows assessment of congestion through venous PD, identifies and stratifies vascular congestion by exploring the IVC, suprahepatic veins (VHS), portal vein (VP), and intrarenal vessels[19,20] (Fig. 1).

The objective of our work is to carry out a review based on the evidence regarding the use of VExUS and its application in the diagnosis and orientation of treatment in CRS.

Material and methods

A search was made for systematic reviews, meta-analyses, observational studies, original studies, articles on evidence-based medicine sites (including MedLine/PubMed, Cochrane, and Google Scholar), published in the last 10 years, in English and in Spanish.

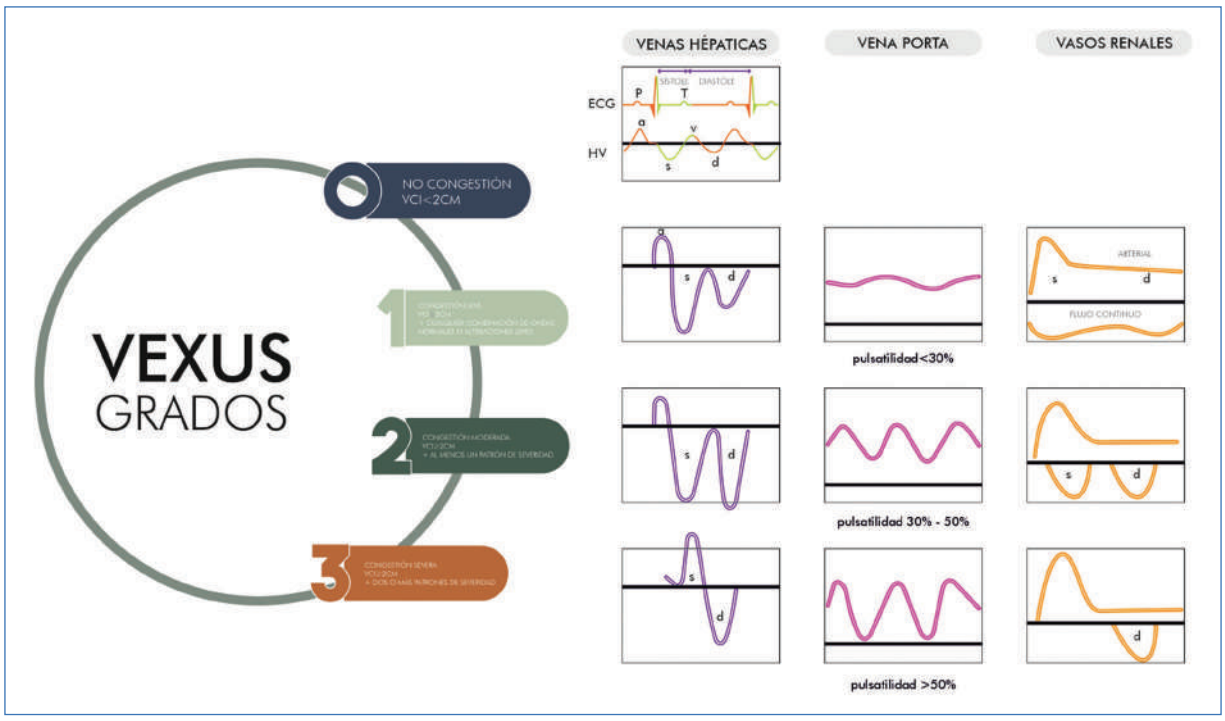

Figure 1. Interpretation of the degrees of congestion (VExUS C). *Adapted from González Delgado DA, Romero González GA, 2021.*

Relevant search keywords and medical subject heading descriptors included:

"VEXUS score", "Point-of-care ultrasound", "Venous Excess Ultrasound Score", "AKI", "CRS", "renal failure", and "Congestive heart failure".

Inclusion/exclusion criteria based on the PICO model were used: [Population] adults with CRS [Intervention] use of POCUS-Score VExUS, [Control] no use of clinical ultrasound, [Outcome] clinical evolution, treatment orientation.

Results

43 results were obtained, only 13 met the inclusion criteria, the rest were excluded or analyzed in the background, as they were not relevant to the objective of the review.

For the analysis of the results, the authors made a description of the articles, as well as a brief summary in the attached table 1.

The evaluation of Doppler congestion by POCUS, and its relationship with AKI has already been studied before the VExUS score: one study prospectively evaluated intrarenal hemodynamics in 217 patients with heart failure, a monophasic pattern (D-only pattern) on intrarenal Doppler was associated with a poorer prognosis compared with a biphasic pattern, which in turn conferred a worse prognosis than a continuous pattern after a mean follow-up of almost 1 year, demonstrating evidence that venous congestion measured at the renal level has an impact in patients with heart failure, those patients without renal congestion do not have cardiovascular events, and yet patients with congestive flow have more complications, exacerbations, and readmissions[21]. In another study, 102 patients were included in the analysis with significant portal flow pulsatility was detected in 38 patients (37.3%) in the week after surgery. During this period, 60.8% developed AKI and 13.7% progressed to severe AKI. Screening for portal flow pulsatility was associated with an increased risk of developing AKI. Portal flow pulsatility and AKI were independently associated[22]. This study reflects the possible relationship between increased abdominal pressure and AKI, we know that in patients with AHF, increased IAP reduction by decongestive therapy may improve renal function, presumably relieving abdominal congestion[23]. In acute HF with ascites, paracentesis reduces intrabadominal pressure and volume overload and therefore improves renal function[24].

Table 1. Summary of the main results of the analyzed studies

Article	Typology	Population/Intervention	Results/Conclusions
Iida N, Seo Y, Sai S, Machino-Ohtsuka T, Yamamoto M, Ishizu T, et al. Clinical implications of intrarenal hemodynamic evaluation by Doppler ultrasonography in heart failure. JACC Heart Fail. 2016;4:674-82.	Clinical study	Prospectively evaluated intrarenal hemodynamics in 217 patients.	A monophasic pattern (D-only pattern) on intrarenal Doppler was associated with a poorer prognosis compared with a biphasic pattern, which in turn conferred a worse prognosis than a continuous pattern after a mean follow-up of almost 1 year, demonstrating evidence that venous congestion measured at the renal level has an impact in patients with heart failure, those patients without renal congestion do not have cardiovascular events, and yet patients with congestive flow have more complications, exacerbations, and readmissions.
Beaubien-Souligny W, Eljaiek R, Fortier A, Lamarche Y, Liszkowski M, Bouchard J, et al. The association between pulsatile portal flow and acute kidney injury after cardiac surgery: a retrospective cohort study. J Cardiothorac Vasc Anesth. 2018;32:1780-7.	Retrospective study	Cohort of cardiac surgery patients. 102 patients	Portal vein pulsatility was associated with increased risk of AKI.
Beaubien-Souligny W, Benkreira A, Robillard P, Bouabdallaoui N, Chassé M, Desjardins G, et al. Alterations in portal vein flow and intrarenal venous flow are associated with acute kidney injury after cardiac surgery: a prospective observational cohort study. J Am Heart Assoc. 2018;7:e009961.	Observational prospective study	145 patients undergoing cardiac surgery.	Portal flow pulsatility and intrarenal flow abnormalities are markers of venous congestion and are independently associated with AKI after cardiac surgery.
Eljaiek R, Cavayas YA, Rodrigue E, Desjardins G, Lamarche Y, Toupin F, et al. High postoperative portal venous flow pulsatility indicates right ventricular dysfunction and predicts complications in cardiac surgery patients. Br J Anaesth. 2019;122:206-14.	Single-center prospective cohort study	Adults undergoing cardiac surgery. A total of 115 patients were included.	Elevated portal flow pulsatility fraction is associated with right ventricular dysfunction, signs of venous congestion and decreased perfusion, and increased risk of major complications. Portal vein Doppler ultrasonography appears promising for risk assessment in the perioperative period.
Beaubien-Souligny W, Rola P, Haycock K, Bouchard J, Lamarche Y, Spiegel R, et al. Quantifying systemic congestion with Point-Of-Care ultrasound: development of the venous excess ultrasound grading system. Ultrasound J. 2020;12:16.	*Post hoc* analysis	145 patients undergoing cardiac surgery.	VExUS C score (Fig. 1) with both moderate (HR: 2.65, CI 1.07-6.60, p = 0.036) and severe (HR: 3.69 CI 1.65-8.24, p = 0.001) congestion was related to the appearance of AKI.
Spiegel R, Teeter W, Sullivan S, Tupchong K, Mohammed N, Sutherland M, et al. The use of venous Doppler to predict adverse kidney events in a general ICU cohort. Crit Care. 2020;24:615.	Observational prospective study in a medical intensive care unit	167 patients of which 121 met the inclusion criteria. Seven patients were excluded due to the inability to obtain ultrasound images, leaving 114 patients for the final analysis.	An S < D pattern on hepatic vein Doppler was shown to predict major adverse renal events at 30 days, with an odds ratio of 4 (95% confidence interval, 1.4-11.2). In contrast, renal parenchymal and portal vein flow abnormalities did not share this association.

(Continues)

Table 1. Summary of the main results of the analyzed studies *(continued)*

Article	Typology	Population/Intervention	Results/Conclusions
Bhardwaj V, Vikneswaran G, Rola P, Raju S, Bhat RS, Jayakumar A, et al. Combination of inferior vena cava diameter, hepatic venous flow, and portal vein pulsatility index: venous excess ultrasound score (VEXUS score) in predicting acute kidney injury in patients with cardiorenal syndrome: a prospective cohort study. Indian J Crit Care Med. 2020;24:783-9.	Prospective study	Patients older than 18 years admitted to the ICU with a provisional diagnosis of cardiorenal syndrome were included in the study. Patients underwent serial determination ultrasound examination until AKI resolved or dialysis was started. Venous Excess Ultrasound Score (VEXUS) comprising inferior vena cava, hepatic vein waveform, and portal vein pulsatility was assessed.	Thirty patients were recruited for the study. Fourteen patients (46.7%) had stage 1 AKI, while eight patients (26.7%) each had stage 2 and 3 AKI. Twenty patients (66.7%) had VEXUS grade III.Resolution of the AKI lesion showed a significant correlation with improvement in VEXUS grade ($p = 0.003$). Similarly, there was a significant association between changes in VEXUS grade and the fluid balance ($p = 0.006$). There was no correlation between central venous pressure (CVP), left ventricular function, and right ventricular function with change in VEXUS grade. Conclusion: The study shows that a combined IVC, hepatic vein, and portal vein classification could reliably demonstrate venous congestion and aid in the clinical decision to perform fluid removal.
Çakal B, Özcan ÖU, Omaygenç MO, Karaca İO, Kızılırmak F, Gunes HM, et al. Value of renal vascular Doppler sonography in cardiorenal syndrome Type 1. J Ultrasound Med. 2021;40:321-30.	Clinical study	A total of 30 patients who presented improvement in creatinine with diuresis (group 1) and 34 patients without improvement (group 2) were analyzed. Group 1 patients had a higher median VII and ARI at admission. A high ARF on admission predicted improvement in serum creatinine levels with diuretic treatment independent of confounding factors in patients with CRS type 1.	Renal vascular Doppler parameters could offer guidance on diagnostic and therapeutic strategies in the prescription of decongestant therapy for AHF.
Argaiz ER, Rola P, Gamba G. Dynamic changes in portal vein flow during decongestion in patients with heart failure and cardio-renal syndrome: a POCUS case series. Cardiorenal Med. 2021;11:59-66.	Clinical case series	Clinical case	Improvement in portal vein pulsatility coincides with resolution of acute kidney injury in patients with decompensated AHF.
Rola P, Miralles-Aguiar F, Argaiz E, Beaubien-Souligny W, Haycock K, Karimov T, et al. Clinical applications of the venous excess ultrasound (VExUS) score: conceptual review and case series. Ultrasound J. 2021;13:32.	Conceptual review article and clinical cases	Series of 5 clinical cases	VExUS can provide stopping points for fluid delivery and identify patients who will benefit from fluid removal.
Torres-Arrese M, de Casasola-Sánchez GG, Méndez-Bailón M, Montero-Hernández E, Cobo-Marcos M, Rivas-Lasarte M, et al. Usefulness of serial multiorgan Point-Of-care ultrasound in acute heart failure: results from a prospective observational cohort. Medicina (Kaunas). 2022;58:124.	Prospective study	Study with 30 patients who were evaluated with a standard protocol of lung ultrasound, echocardiography, inferior vena cava (IVC), and hepatic, portal, intrarenal, and femoral Doppler flow patterns on admission and on the day of discharge.	Of other parameters obtained. Performing serial point-of-care multiorgan ultrasound scans may help us better identify patients with high and intermediate probability of pulmonary hypertension and acute heart failure. Currently proposed multiorgan venous Doppler scanning protocols, such as VE × US score, should be further studied before expanding their use in patients with AHF.

(Continues)

Table 1. Summary of the main results of the analyzed studies *(continued)*

Article	Typology	Population/Intervention	Results/Conclusions
Argaiz ER, Cruz N, Gamba G. Evaluation of rapid changes in haemodynamic status by Point-of-Care Ultrasound: a useful tool in cardionephrology. Clin Kidney J. 2022;15:360-2.	Clinical cases	Description of two clinical cases.	Vexus allows to follow rapid hemodynamic changes in patients on HD with PHT with each ultrafiltration we see how the portal vein improves. We know if the patient responds to substitution therapy or heart failure due to av fistula rapid hemodynamic changes, follow the patients during our therapies.
Torres-Arrese M, de Casasola-Sánchez GG, Méndez-Bailón M, Montero-Hernández E, Cobo-Marcos M, Rivas-Lasarte M, et al. Usefulness of serial multiorgan Point-Of-Care ultrasound in acute heart failure: results from a prospective observational cohort. Medicina (Kaunas). 2022;58:124.	Prospective study	74 AHF patients with a NT-proBNP level above 500 pg/mL were prospectively recruited. A multiorgan ultrasound assessment (lung, inferior vena cava, Doppler of hepatic, portal, intrarenal, k and femoral veins) were performed at admission, discharge, and follow-up (for 90 days).	VExUS score does not contribute to guide therapy or the predic-tion of complications, compared to the presence of an inferior vena cava > 2 cm, a venous mo-nophasic intrarenal pattern or a pulsatility > 50% of the portal vein in AHF patients.

VExUS: Venous Excess Ultrasound Grading System.

We can consider the predecessor of the VEXUS protocol the prospective study of 145 cardiac surgery patients[20], in which portal pulsatility was associated with an increased risk of AKI. Hepatic and renal Doppler ultrasound evaluations were performed before surgery, on admission to the intensive care unit, and daily for 3 days after surgery. The primary statistical analysis was performed using the proportional hazards model for the time-dependent variables. Of the 145 patients included, 49 patients (33.8%) developed ARF after cardiac surgery. Detection of portal flow pulsatility was associated with increased risk of AKI, as well as severe intrarenal venous flow abnormalities. These associations remained significant in multivariable models.

Multiple studies have evaluated the clinical utility of waveform Doppler in isolation: Eljaiek et al. demonstrated that a portal vein pulsatility fraction ≥ 50% was associated with increased intraoperative fluid balance as well as complications[25].

It is mandatory to describing the study that gave rise to the development of the different VExUS phenotypes, Beaubien-Souligny et al. developed a protocol for the measurement of venous congestion beginning POCUS, called VExUS, the original study, consisting of a post-hoc analysis of one of a cohort of 145 patients undergoing cardiac surgery, patients with renal failure were excluded. disease, delirium, cirrhosis, portal thrombosis or severe kidney disease (GFR < 15 mL/min or dialysis) described that the VExUS C score, both moderate and severe congestion, was related to the appearance of AKI[19]. This study showed that VExUS is a score that has high specificity and high positive predictive value to know that patients are going to develop congestive AKI, the main conclusion was that VExUS score is more specific than its individual components, and more specific than invasively measuring venous pressure. It was based on a prospective study of cardiac surgery patients[20], in which portal pulsatility was associated with an increased risk of AKI. Hepatic and renal Doppler ultrasound evaluations were performed before surgery, on admission to the intensive care unit, and daily for 3 days after surgery.

The addition of these markers to the preoperative risk factors and the measurement of central venous pressure on admission to the intensive care unit improved the prediction of AKI, which allowed us to conclude that portal flow pulsatility and intrarenal flow abnormalities they are markers of venous congestion and are independently associated with AKI after cardiac surgery. These tools could offer valuable information for developing strategies to treat or prevent congestive CRS after cardiac surgery.

In a prospective study in a medical intensive care unit, an S < D pattern on hepatic vein Doppler was shown to predict major adverse renal events at 30 days. In contrast, renal parenchymal and portal vein flow abnormalities did not share this association[26].

Another interesting prospective study on the use of Score VEXUS and CRS, observed 30 adults with CRS admitted to the ICU, shows that a combined IVC, hepatic vein, and portal vein classification could reliably demonstrate venous congestion and id in the clinical decision to perform fluid removal[27].

Another cohort of 30 patients, CRS type 1 cases were identified among patients hospitalized for decompensated heart failure. Serial measurements of the renal venous impedance index and the arterial resistance index were calculated using PD ultrasound. The results of this clinical trial suggested that both the renal arterial resistance index and intrarenal venous flow could offer guidance on the diagnosis and treatment of CRS type 1[28].

In another case series from 2021, Argaiz et al. demonstrated that the improvement in portal vein pulsatility coincides with the resolution of AKI in patients with AHF, it is described how VExUS is useful in the orientation of patients with difficult volume management, with impaired function renal, with apparent systemic venous congestion that raises doubts about whether volume is needed because the priority dysfunction is that of the right ventricle, requiring preload or if the congestion is so high that it causes intracapsular tamponade[29].

Rola et al. presented a case series illustrating how the assessment of venous splanchnic congestion can be critically important in a wide variety of clinical settings. The unclear concept of "volume status" remains a challenge for clinicians in general due to the limitations of the physical examination. Indeed, in many patients, it may not be possible to identify the presence of venous congestion associated with possible end-organ dysfunction without invasive monitoring or ultrasonographic evaluations, describing how VExUS as a window into venous pathophysiology could be key to achieving accurate fluid management and highlight the importance of the need for increased knowledge about VExUS assessment for all frontline clinicians involved in making daily decisions about fluid balance management[30].

The use of VExUS in adults with heart failure, different variables were analyzed in a prospective study with 30 patients[31], who were evaluated with a standard lung ultrasound, echocardiography, IVC, and liver, portal, intrarenal, and femoral Doppler flow patterns on admission and on the day of discharge. However, in AHF, there is an underestimation of creatinine at the onset of the disease due to hemodilution, so it is not a parameter on which we should base therapeutic changes[32]. They described that there was not so much evidence in patients with HF, and that it is probably not useful in this cohort to apply the VExUS score but the PV pulsatility alone, they also described the correlation of the VExUS determination with other patterns, the performance of ultrasound serial point-of-care multiorgan testing could help to better identify patients with high and intermediate probability of pulmonary hypertension and AHF. Currently proposed multi-organ venous Doppler protocols, such as VExUS scoring, need to be further studied before expanding their use in patients with AHF.

On the other hand, Argaiz also describes the two clinical cases in which the application of Vexus makes it possible to follow rapid hemodynamic changes in patients with pulmonary hypertension (PTH)[33].

The most recent of the studies analyzed in this review offers us a prospective study that included 74 AHF patients with a NT-proBNP level above 500 pg/mL. Then, a multiorgan ultrasound assessment, concluding that VExUS score does not help to guide therapy and is not even useful to guide the treatment of patients with AHF, compared with the presence of an IVC > 2 cm, a monophasic intrarenal venous pattern, or a pulsatility > 50% from the portal vein, the authors also conclude that VExUS adds complexity to the evaluation and prognosis of patients with AHF without clear benefit[31].

There is an ongoing prospective observational study involving 60 patients with no results yet in which investigators hypothesize that the VExUS score might be of value in predicting response to diuretic therapy, assessing volume status of patients and predict mortality in cardiorenal patients[34].

In a prospective study that included 205 patients who underwent right heart catheterization with a previous diagnosis or suspicion of pulmonary hypertension, Husain-Syed et al.[35] found that a severely abnormal intrarenal venous flow pattern predicted the endpoint of morbidity or mortality, noting that congestive organ injury is seen in both pressure and volume overloads.

As previously described Beaubien-Souligny et al. looked at several classification systems for venous congestion and validated the VEXUS protocol by concluding that two severe alterations in hepatic and portal vein flow patterns and an IVC diameter > 2 cm are associated with a high incidence of AKI after of cardiac surgery.

Du et al.[36] proposed monitoring hepatic venous velocity to assess fluid response in patients with shock and found that D wave velocity change of > 21% is indicative of fluid nonresponsiveness.

The presence of AKI in CRS is not due only to venous congestion, but also to other contributing factors. The improvement of the VEXUS grade with the resolution of the AKI should not be taken simply as a decrease in venous congestion.

The concept is very exciting, but before it can be labeled the first tool in the arsenal, it needs to be validated on various subsets of patients and also with various degrees of experience of the performer.

VExUS has been validated mainly in CRS and critically ill patients in such a way that, in CRS, the study of VR flow through the PD showed a better correlation with congestion and was correlated with increased RA pressure measured by right catheterization, accompanied by worse outcomes in congestive patients compared to those with mild congestion or those without it. On the other hand, guiding depletive therapy through VExUS in the critically ill patient with CRS was significantly correlated with renal recovery in patients with AKI[37].

Alterations in PD patterns without congestion can be observed, for example in patients with low muscle mass index, liver parenchymal abnormalities, severe tricuspid regurgitation or advanced chronic disease[38].

Discussion

In the literature there is considerable evidence of VExUS in cohorts of post-surgical patients, but in fact we see more patients with acute or acute chronic HF, with sepsis, with hemorrhagic shock, cardiogenic and with consequent CRS of other etiologies and another phenotype, within this group of patients most frequent in our day to day, there is still little evidence of the use of VExUS. In these patients it is also essential to know how to recognize fluid tolerance and when to stop the fluid intake because it will be deleterious, and even when to withdraw fluids and start depletive therapy. It is in this context where the importance of the VExUS score is striking, which will allow us to observe accessible organs that will inform us of the congestive state of the patient with different patterns of degrees of congestion, as well as guide the decongestion treatment either through drugs or ultrafiltration[39]. But beyond the definition of euvolemia, more practical questions focus on when to give or when to withdraw fluid, as a routine parameter in the evaluation of AKI to help the clinical decision to add/increase the dose of diuretic support and/or inotropic.

Although VExUS may not provide much information about fluid requirements, it can provide stopping points for fluid resuscitation and identify patients who are likely to tolerate and benefit from fluid removal.

Despite the fact that VExUS has been increasingly present in the literature since its first publication, it is necessary to generate evidence to know if this score could be useful to manage, assess and adjust the treatment of our main cohort of patients.

Other scales adapted to our patients may be necessary, which could be sufficient with the integration of VExUS, for example, the use of lung ultrasound, or perhaps portal pulsatility would be sufficient, or in the specific case of congestive patients with CRS, Could renal pulsatility be enough?

Another area where future studies will be needed is in patients with chronic kidney disease to assess the impact of venous Doppler-guided ultrafiltration on practical outcomes, such as heart failure-related hospitalizations and blood pressure control[40] and to assess how to best integrate VExUS into clinical care and the impact of such an approach on measurable outcomes[41].

In our daily context, where we come across patients with cirrhosis, portal hypertension, arrhythmias, we must be cautious as there may be false positives and negatives.

Cardiorenal medicine is one of those areas where it would be necessary to clarify the usefulness of POCUS[41]. It is well known that persistent congestion is associated with worse outcomes in patients with CRSs. Unfortunately, conventional physical examination findings are not always reliable in assessing volume status. In this context, POCUS and more specifically VExUS has emerged as an attractive “enhancement” for the clinical examination of the congestive patient, however, future studies are needed to assess how to better integrate VExUS into clinical care and the impact of such an approach on patients.

Several clinical trials testing this protocol in various patient groups are underway and are expected to shed light on some of the unknowns by providing evidence for the use of VExUS to address our patients with CRS and congestion.

Another question that we could ask ourselves would be: Would the modification of the original VEXUS protocol make it valid for the majority of the patients that we observe in our daily practice? perhaps the results would be different if larger and preferably multicentre studies were conducted, but until then, we can gain more experience using the protocol but also continue to observe and integrate into the clinical setting.

Conclusion

In conclusion, most of the studies carried out correspond to post-surgical patients, and despite the fact that VExUS is increasingly present in the literature, it is necessary to generate evidence to know if it could be useful to manage, assess, and adjust the treatment of our main cohort of patients.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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