Admission high-sensitivity cardiac troponin levels as a prognostic indicator for in-hospital mortality rates in the elderly and very elderly COVID-19 patients

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ABSTRACT

Background: Elevation of cardiac troponin (cTn) is associated with the worst prognosis not only in cardiovascular disease but also in non-cardiovascular disease. The aim of this study is to verify if cTn has a prognostic role in elderly and very elderly coronavirus disease 2019 (COVID-19) patients.

Methods: This study enrolled consecutive COVID-19 elderly patients hospitalized at INRCA hospital, with available admission high sensitivity cardiac troponin T (HS-cTnT) level. Patients were divided into three groups based on HS-cTnT level: group A (Hs-cTnT $\leq$ 40 pg/ml), group B (Hs-cTnT 41-100 pg/ml), and group C (Hs-cTnT $\geq$ 101 pg/ml). The correlation between HS-cTnT levels and mortality rates was analyzed.

Results: 461 patients (mean age 86 years; 59% female) were divided into group A (261 patients), group B (129 patients), and group C (71 patients). Group C resulted significantly older, more affected by heart failure, chronic obstructive pulmonary disease, chronic kidney disease, and dementia, and with higher levels of creatinine, C-reactive protein, pro-calcitonin, interleukin-6, ferritin, NT-proBNP, D-dimer then group A and group B. Mortality rate increased significantly across groups (group A: 18.4%; group B: 36.4%; group C: 62.0%; *p*<0.001). Group C had a significant increase in mortality risk compared to group A, both univariate analysis (HR 3.78) and multivariate analysis (model 2 HR 3.10; model 3 HR 3.59; model 4 HR 1.72).

Conclusion: HS-cTnT has demonstrated a prognostic role in elderly and very elderly COVID-19 patients. HS-cTnT is a simple and inexpensive laboratory exam that gives clinicians important information on mortality risk stratification.

1. Introduction

Cardiac troponin (cTn) is a protein of the contractile apparatus of cardiac myocytes. It is released into the circulation after myocardial cell injury. There are two subtypes of cTn: cardiac troponin T (cTnT) and cardiac troponin I (cTnI) (Forman et al., 2020). For their tissue specificity, cTnT and cTnI assay are the principal blood tests for diagnosing acute coronary syndrome (ACS) or other acute cardiac damage. For this

reason, they are frequently used in screening blood tests in emergency room admission (Conway et al., 2021). With the advent of the high sensitivity (Hs) assay, the specific role of cTn in acute myocardial injury diagnosis is decreased. In fact, with Hs-cTn assay, it is possible to detect a minimal concentration of circulating protein in the absence of acute cardiac damage. Hs-cTn elevation occurred not only in ACS but also in other non-ischemic cardiac injuries (acute or chronic), in a wide spectrum of non-cardiac pathologies (infection disease/sepsis, chronic

kidney disease, stroke, subarachnoid hemorrhage, critically ill patients, after chemotherapeutic drugs use), and could appear in apparently healthy people (Thygesen et al., 2018; Willeit et al., 2017).

Especially in elderly patients, the Hs-cTn assay loses even more specificity for diagnosing acute myocardial injury due to more causes of non-specific Hs-cTn elevation, such as age and comorbidity (Sedighi et al., 2019, 2020; Olivieri et al., 2012). In this population, HS-cTn value has demonstrated a prognostic capacity in different clinical scenarios and not only in cardiovascular disease. This HS-cTn capacity moved its use from diagnostic to prognostic tool (Savonitto et al., 2012; Chen et al., 2019; Ishigami et al., 2019; McKechnieT et al., 2021).

Since December 2019 Coronavirus disease-2019 (COVID-19) pandemic has dominated the world clinical scene. COVID-19 is the clinical manifestation of severe acute respiratory syndrome coronavirus 2 (SarsCoV-2) infection. COVID-19 patients with the worst prognosis are older and more comorbid patients. The reason why COVID-19 patients with similar clinical characteristics (age, comorbidities, grade of pneumonia, etc.) often do not have the same prognosis is unknown. It is known that several cardiovascular complications can occur during COVID-19 infection and influence patient prognosis: direct myocardial injury (ischemic and non-ischemic), arrhythmic events, heart failure, and vascular events due to coagulation disorder (Kwenandar et al., 2020). Also, in COVID-19, the elevation of cTn is associated with the worst prognosis. Increased cTn value can be due not only to direct cardiac damage during COVID-19 but also to pre-existing cardiovascular diseases or other comorbidities (Long et al., 2020; Gaze, 2020; Shi et al., 2020; Sandoval et al., 2020). This last mechanism can be predominant in elderly and very elderly patients, but clinical evidence on this topic is scarce.

This study aims to verify if Hs-cTnT entry levels have a prognostic role and risk-stratification capacity in elderly and very elderly patients affected by SarsCov-2 infection.

2. Methods

2.1. Study population

The study was a retrospective cohort analysis involving consecutive geriatric patients (over 65 years old (y)) hospitalized for COVID-19 at INRCA Hospital of Ancona, Italy, from March 2020 to June 2021. Clinical data (medical history, clinical parameters, laboratory analysis and clinical events) of enrolled patients derived from computerized medical records of the hospitalization. Diagnosis of COVID-19 was confirmed by a positive polymerase chain reaction (PCR) test of a nasopharyngeal swab. The only exclusion criterion was the absence of the Hs-cTnT entry level.

Ethics approval was obtained from the Ethics Committee of the IRCCS-INRCA, Ancona, Italy (reference number CE-INRCA-20008). The protocol has been registered under the ClinicalTrial.gov database (reference number NCT04348396).

Enrolled patients are divided in three groups based on Hs-cTnT entry levels: group A (low-levels) Hs-cTnT ≤ 40 pg/ml, group B (mid-levels) Hs-cTnT 41-100 pg/ml; group C (high-levels) Hs-cTnT ≥ 101 pg/ml. HS-cTnT is dosed by Elecsys® Troponin T hs STAT assay within six hours from hospital admission. Age-specific 99th percentile, normal troponin range levels for HS-cTnT in our laboratory is ≤ 40 pg/ml for over 85 y patients. These levels correspond to study group A. Considering the study population characteristics and the role of age and comorbidities on HS-cTnT levels (Sedighi et al., 2019, 2020; Olivieri et al., 2012), we have chosen to consider levels of Hs-cTnT ≥ 101 pg/ml (equal to 2.5-fold of the normal limit of 40 pg/ml) to define high Hs-cTnT levels (group C). Patients with Hs-cTnT 41-100 pg/ml were defined as subjects with mid-levels (group B).

All patients were tested for the following comorbidities: hypertension (HT), coronary artery disease (CAD), heart failure (HF), atrial fibrillation (AF), diabetes mellitus (DM), chronic obstructive pulmonary

disease (COPD), stroke history, cancer history, chronic kidney disease (CKD).

At the admission entry, parameters like arterial pressure, heart rate, peripheral oxygen saturation, and body temperature have been recorded. The blood sample was analyzed for creatinine, C-reactive protein (CRP), pro-calcitonin (PCT), interleukin-6 (IL-6), ferritin, N-terminal pro-brain natriuretic peptide (NT-proBNP) and D-dimer.

The definition of CKD was based on the estimated glomerular filtration rate (eGFR) <60 ml/min obtained by CKD-EPI formula.

To test the prognostic role of admission HS-cTnT, in-hospital mortality was assessed as the primary outcome.

2.2. Statistical analysis

Continuous variables were reported as median and interquartile range or mean and standard deviation based on their distribution (assessed using the Shapiro-Wilk test). Categorical variables were expressed as absolute frequency and percentage. Comparison of variables among groups was performed by the Kruskal-Wallis equality-of-populations rank test or One-way analysis of variance (ANOVA) for continuous variables as appropriate and by the Chi-square test for categorical variables. The association of Hs-cTnT entry value groups with mortality during hospital stay was explored by Kaplan-Meyer curves and assessed by the log-rank test of equality. Then, Cox proportional hazard models were built to obtain adjusted estimates of the association between exposure variables and study outcomes. A 2-tailed *P* value <0.05 was considered significant. Data were analyzed using STATA version 15.1 (StataCorp, College Station, TX).

3. Results

Four hundred sixty-one COVID-19 patients (59% female sex) with a mean age of 86 (83−91) y were enrolled. Based on Hs-cTnT entry levels population was divided as follows: 261 patients in group A, 129 patients in group B, and 71 patients in group C. Group C patients were significantly older than other groups (mean age respectively 85 y (81−89) for group A, 88 y (84−93) for group B and 89 y (84−93) for group C with *p* <0.001). No significant differences in the sex category were noted between all groups. Respect to comorbidities HF (16.9% vs 24.8% vs 43.7%; *p*<0.001), COPD (10.7% vs 18.6% vs 21.1%; *p*=0.027), CKD (11.9% vs 31.0% vs 43.7%; *p*<0.001) and dementia (31.0% vs 36.4% vs 52.1%; *p*=0.004) were more present in higher levels HS-TnT groups. For AF there was a trend (23.4% vs 31.0% vs 35.2%, *p*= 0.076), but this finding did not reach statistical significance. There were no differences for other comorbidities (HT, CAD, DM, stroke, and cancer) between all groups. Complete population characteristics are shown in Table 1.

Regarding clinical admission parameters, no differences between groups were observed for heart rate, body temperature, and peripheral oxygen saturation. A significant statistical difference between groups was noted for arterial blood pressure, both systolic blood pressure (group A 137.4 ± 19.7 mmHg; group B 136.6 ± 22.5 mmHg; group C 124.5 ± 23.3 mmHg; *p*<0.001) and diastolic blood pressure (group A 75.9 ± 12.2 mmHg; group B 75.4 ± 12.3 mmHg; group C 71.6 ± 12.3 mmHg; *p*=0.033). There were significant differences between groups for laboratory tests performed (creatinine and eGFR, CRP, PCT, IL-6, ferritin, NT-proBNP, D-dimer), as described in Table 1. A significant difference between groups was observed in mortality rate (group A: 18.4%; group B: 36.4%; group C: 62.0%; *p*<0.001) without a difference in mean recovery length.

As can be seen in the Kaplan-Meier curve (Fig. 1), a higher in-hospital mortality rate was observed in patients with high-levels HS-cTnT (group C) compared with mid-levels HS-cTnT (group B) and low-levels HS-cTnT (group A). Log-rank test for equality of survivor functions was significant (*p*<0.001).

In univariate analysis (model 1) respect group A (low-levels HS-cTnT) HR for death was 1.87 (95%CI 1.25−2.80) for group B (mid-

Table 1

The study population's demographic, clinical, and laboratory characteristics stratified by HS-cTnT entry levels. Hypertension (HT), coronary artery disease (CAD), heart failure (HF), atrial fibrillation (AF), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), diastolic blood pressure (dia press), systolic blood pressure (sys press), Oxygen (O2), C-reactive protein (CRP), pro-calcitonin (PCT), interleukin-6 (IL-6).

	Number of patients n=461	HS-cTnT ≤40 n=261	HS-cTnT 41-100 n=129	HS-cTnT ≥101 n=71	p
Age, median (IQR)	86(83-91)	85(81-89)	88(84-93)	89(84-93)	<0.001
Female sex, n(%)	272(59%)	166(63.6%)	67(51.9%)	39(54.9%)	0.066
HT, n (%)	305(66.2%)	171(65.5%)	87(67.4%)	47(66.2%)	0.931
CAD, n (%)	43(9.3%)	18(6.9%)	17(13.2%)	8(11.3%)	0.111
HF, n (%)	107(23.2%)	44(16.9%)	32(24.8%)	31(43.7%)	<0.001
AF, n (%)	126(27.3%)	61(23.4%)	40(31%)	25(35.2%)	0.076
DM, n (%)	96(20.8%)	52(19.9%)	32(24.8%)	12(16.9%)	0.362
COPD, 14n (%)	67(.5%)	28(10.7%)	24(18.6%)	15(21.1%)	0.027
Stroke, n (%)	33(7.2%)	18(6.9%)	11(8.5%)	4(5.6%)	0.727
CKD, n (%)	102(22.1%)	31(11.9%)	40(31%)	31(43.7%)	<0.001
Dementia, n (%)	165(35.8%)	81(31%)	47(36.4%)	37(52.1%)	0.004
Cancer, n (%)	74(16.1%)	49(18.8%)	15(11.6%)	10(14.1%)	0.173
Dia_press, mean±sd	75.1±12.3	75.9±12.2	75.4±12.3	71.6±12.3	0.033
Sys_press, mean±sd	135.2±21.5	137.4±19.7	136.6±22.5	124.5±23.3	<0.001
Heart rate, median (IQR)	77(68-89)	76(67-89)	76(70-90)	79.5(68-88)	0.276
O2 saturation, median (IQR)	96(94-97)	96(94-97)	96(94-97)	96(95-98)	0.258
Temperature, median (IQR)	36.3(36-36.65)	36.4(36-36.7)	36.4(36-36.7)	36.2(36-36.5)	0.204
Creatinine, median (IQR)	0.9(0.7-1.3)	0.8(0.6-1)	1.1(0.7-1.5)	1.4(0.9-2.4)	<0.001
eGFR, median (IQR)	69(45-84)	80(58-86)	59(38-80)	37.5(24-58)	<0.001
CRP, median (IQR)	3.65(1.29-8.975)	2.86(1.15-7.38)	4.12(1.47-9.72)	6.085(2.87-13.07)	<0.001
PCT, median (IQR)	0.09(0.05-0.26)	0.05(0.05-0.15)	0.14(0.05-0.39)	0.31(0.15-1.65)	<0.001
IL-6, median (IQR)	34.9(14-77.7)	25.25(11.3-51.15)	45.7(21.1-92.8)	94.1(40.55-159.15)	<0.001
Ferritin, median (IQR)	561(317-998)	526(292-940)	543.5(340-999.5)	802(420-1601)	0.015
NT-proBNP, median (IQR)	1529(567.5-4169.5)	787(341-1884)	2286(1199-5797)	7886.5(3044-21250)	<0.001
D-dimer, median (IQR)	1115(660-2255)	1030(600-2015)	1340(660-2320)	1650(920-4180)	0.002
Lenght of stay, median (IQR)	14(9-22)	14(10-21)	14(9-23)	12(5-23)	0.116
Death, n (%)	139(30.2%)	48(18.4%)	47(36.4%)	44(62.0%)	<0.001
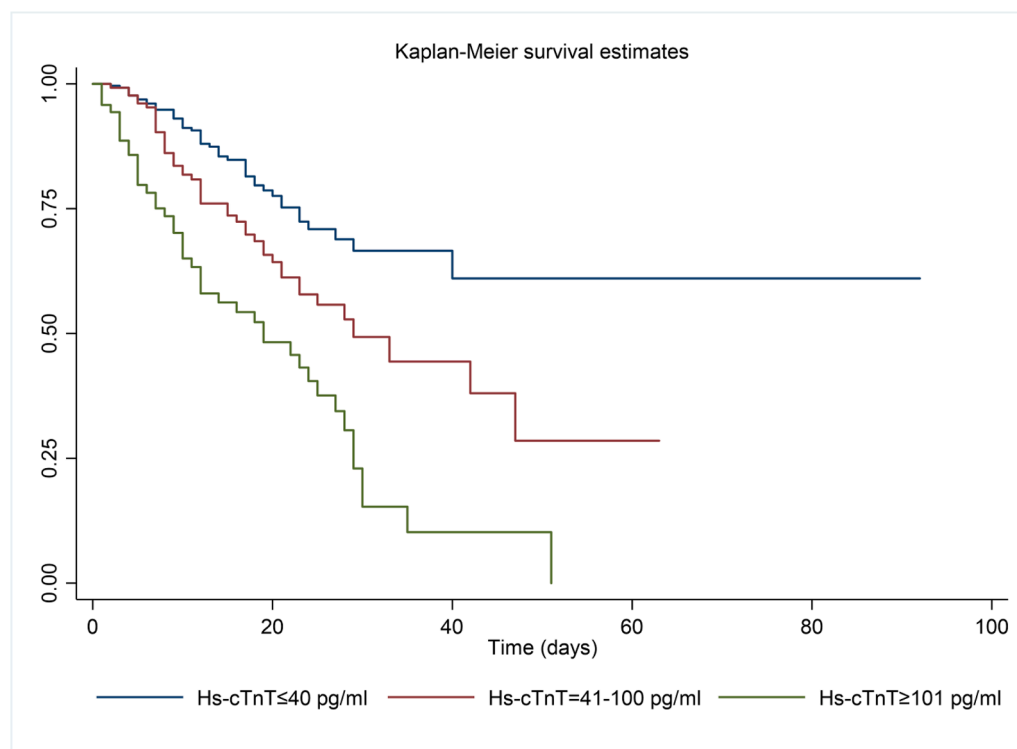
Fig. 1. Kaplan-Meier curve for in-hospital mortality according to HS-cTnT entry levels. Log-rank test for equality of survivor functions (p<0.001).

levels HS-cTnT) and 3.78 (95%CI 2.51–5.70) for group C (high-levels HS-cTnT). In multivariate cox regression analysis (Table 2), the HR for mortality in the high-levels HS-cTnT group (group C) respect reference (group A) was 3.10-fold (95% CI 2.03–4.72) after correction for sex and age (model 2), 3.59-fold (95% CI 2.26–5.71) after correction for sex, age and comorbidities (model 3), 1.72-fold (95% CI 1.01–2.95) after

correction for sex, age, comorbidities and laboratory tests (model 4). There was a significant increase in mortality risk also for mid-levels group (group B) respect group A in model 2 (correction for sex and age) and model 3 (correction for sex, age, and comorbidities). There was no independently increased risk for mortality in group B with respect reference to model 4 correction (model 3 + laboratory tests).

Table 2

Multivariate Cox regression analysis. Model 1: univariate. Model 2: after correction for age and sex. Model 3: after correction for model 2 + comorbidities (HT, CAD, HF, AF, DM, COPD, stroke, CKD, dementia, cancer). Model 4: after correction for model 3 + laboratory tests (creatinine and eGFR, CRP, PCT, IL-6, ferritin, NT-proBNP, D-dimer).

	Model 1 HR(95%CI)	Model 2 HR(95%CI)	Model 3 HR(95%CI)	Model 4 HR(95%CI)
Group A (HS-cTnT ≤40)	reference	reference	reference	reference
Group B (HS-cTnT 41-100)	**1.87(1.25-2.80)**	**1.53(1.01-2.32)**	**1.55(1.02-2.37)**	1.13(0.72-1.75)
Group C (HS-cTnT ≥101)	**3.78(2.51-5.70)**	**3.10(2.03-4.72)**	**3.59(2.26-5.71)**	**1.72(1.01-2.95)**

4. Discussion

Since the SarsCov-2 pandemic started, several clinical trials demonstrated cardiovascular complications in about 20% of COVID-19 patients (Shi et al., 2020). Heart damage rarely appears as a consequence of type 1 ischemic heart disease (plaque rupture or coronary thrombus), but more often emerges as a consequence of other pathological mechanisms such as type 2 ischemic heart disease due to severe hypoxia secondary to SarsCov2 pneumonia, cytokine storm with inflammatory damage-causing myocarditis or stress cardiomyopathy and pulmonary embolism (Tersalvi et al., 2020). Different studies demonstrated that increasing cTn levels is associated with the worst prognosis (Lombardi et al., 2020). This aspect is important because cTn is an easy laboratory test to perform and can help clinicians to predict in-hospital mortality risk. Unfortunately, there is scarce clinical evidence on this topic of elderly and especially very elderly patients, despite being COVID-19 patients with higher mortality.

This study showed a significant association between HS-cTnT elevation and in-hospital mortality. The study involves very elderly patients (mean age is 86 y) that are the population category more involved by a severe form of COVID-19 and who most often require hospitalization. Previous studies were shown a dichotomous relationship between cTnI elevation and mortality without different rates in mortality with increasing cTnI levels (De Marzo et al., 2021; García de Guadiana-Romualdo et al., 2021). Interestingly, in this study mortality rates increased significantly across HS-cTnT entry levels groups (group A: 18.4%; group B: 36.4%; group C: 62.0%; p<0.001). Other than acute cardiac involvement COVID-19-related, increasing HS-cTnT levels can be linked to the age and comorbidities of these patients (Sedighi et al., 2019, 2021). This mortality rate trend across groups can reflect the increase in the complexity of the patient (Group C was significantly older, more affected by HF, COPD, CKD, and dementia, and with higher levels of creatinine, CRP, PCT, IL-6, ferritin, NT-proBNP, D-dimer then group A and group B) and this is known to be associated with a worse prognosis in COVID-19 (Inciardi et al., 2020; Onder et al., 2020).

In this study, the highest HS-cTnT entry-level, measured in group C, is significantly associated with a high mortality rate and is an independent risk factor for mortality. In fact, group C has a significant increase in mortality risk with respect to group A in univariate analysis (HR 3.78). It maintains significativity after different corrections in multivariate analysis (model 2 HR 3.10; model 3 HR 3.59; model 4 HR 1.72). These high HS-cTnT levels (≥ 101 pg/ml) are probably linked to direct heart damage during COVID-19. The data of this study go along with data already present in the literature that showed a worse prognosis in COVID-19 patients with cardiac complications. The results of this study demonstrated the extension of this observation also in the group of very elderly patients that are particularly vulnerable to COVID-19 infection.

Group B of subjects resulted in a mortality rate higher than group A (36.4% vs 18.4%, p<0.001) and lower than group C (36.4% vs 62.0%, p<0.001). Mid-level HS-cTnT elevations are an independent risk factor

for mortality respect reference (group A) in multivariate cox regression analysis model 2 (HR 1.53) and model 3 (HR 1.55). In model 4 (after correction for other laboratory tests), mid-level HS-cTnT elevation loses his independently prognostic capacity. This aspect can be explained by the fact that these mid-levels of HS-cTnT elevation (41−100 pg/ml) in elderly and very elderly patients are probably not due to direct COVID-19 cardiac involvement but are more probably an expression of aging, chronic comorbidities and systemic inflammation (Sedighi et al., 2019, 2020; Olivieri et al., 2012; Sedighi et al., 2021).· Inflammation plays an important role in aging, especially in frailty development (inflamm-aging theory) (Franceschi et al., 2000). Chronic inflammation can explain elevated cTn levels via complex processes involving oxidative stress, disturbed protein synthesis and degradation, mitochondrial damage, apoptosis, fibrosis, myocardial inflammation, and endothelial dysfunction. Frail older adults present more comorbidities, chronic inflammation, subclinical heart damage, and, therefore, more elevated circulating cTn levels (Franceschi et al., 2000, 2018; Livshits & Kalinkovich, 2019; Soysal et al., 2020). SarsCov-2 infection can exacerbate this condition with an acute inflammation process and increase HS-cTnT levels without direct cardiac injury. In fact, the prognostic capacity of Hs-cTnT in group B (mid-levels elevation), is not separated from other laboratory tests linked to inflammation (CRP, PCT, IL-6 and ferritin) and chronic comorbidities (NT-proBNP, D-dimer, and creatinine) (Buicu et al., 2021; Domingues et al., 2020; Pietrobon et al., 2020; Müller & Di Benedetto, 2021).

The limitation of this study could be that data HS-cTnT of patients enrolled in this study was measured only once at patient admission. This limitation made it impossible to define if HS-cTnT increasing during COVID-19 infection was due to ASC (type 1 or type 2) or to non-ischemic COVID-19 heart damage or it is related to different patient's comorbidities. With overtime monitoring of HS-cTnT levels will be useful to better understand the relationship between cTnT, heart involvement, comorbidity and mortality.

5. Conclusion

In conclusion, this study has demonstrated the utility of evaluating HS-cTnT at hospitalization for elderly and very elderly COVID-19 patients. HS-cTnT (or other HS-cTn) is an available and not expensive blood test on COVID-19 patients that gives clinicians important prognostic information. In fact, an entry-level HS-cTnT above 100 pg/ml is an independent predictor of in-hospital mortality.

Complete knowledge of cardiac damage mechanisms in COVID-19 will help understand if the mortality rate linked to the mid-level elevation of HS-cTnT is due to direct COVID-19 mild heart complication or the chronic subclinical heart damage correlated with frailty and comorbidities in this very elderly population. The type of aging, fit or frail, correlated to inflamm-aging theory, can explain why patients with similar clinical characteristics often have different prognoses. HS-cTn and other laboratory tests (CRP, PCT, IL-6, ferritin, NT-proBNP, D-dimer and creatinine) can help clinicians make more accurate in-hospital mortality risk stratification of elderly and very elderly COVID-19 patients.

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