

Characterization of NT-proBNP in a large cohort of COVID-19 patients

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Aims

Extensive research regarding the association of troponin and prognosis in coronavirus disease 2019 (COVID-19) has been performed. However, data regarding natriuretic peptides are scarce. N-terminal pro B-type natriuretic peptide (NT-proBNP) reflects haemodynamic stress and has proven useful for risk stratification in heart failure (HF) and other conditions such as pulmonary embolism and pneumonia. We aimed to adequately characterize NT-proBNP concentrations using a large cohort of patients with COVID-19, and to investigate its association with prognosis.

Methods and results

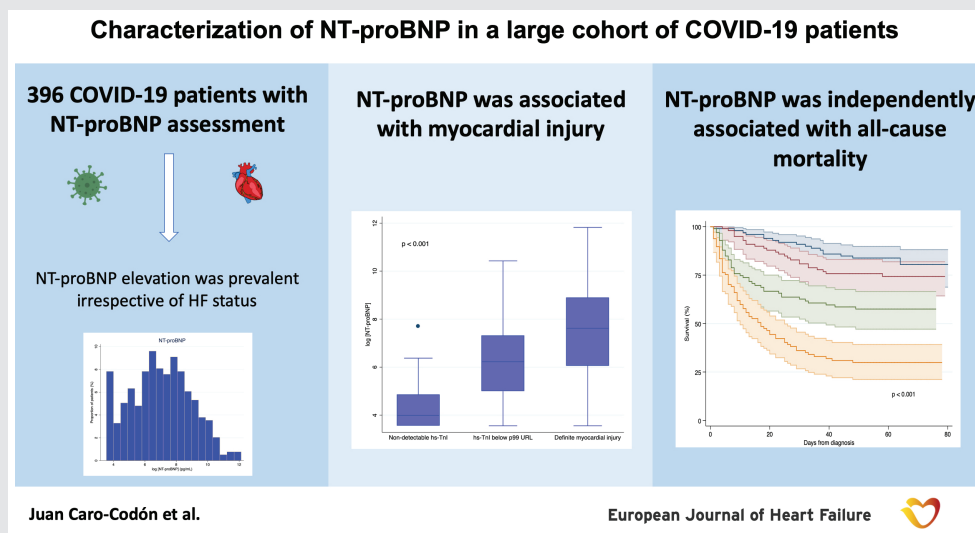
Consecutive patients with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and available NT-proBNP determinations, from March 1st to April 20th, 2020 who completed at least 1-month follow-up or died, were studied. Of 3080 screened patients, a total of 396 (mean age 71.8 ± 14.6 years, 61.1% male) fulfilled all the selection criteria and were finally included, with a median follow-up of 53 (18–62) days. Of those, 192 (48.5%) presented NT-proBNP levels above the recommended cut-off for the identification of HF. However, only 47 fulfilled the clinical criteria for the diagnosis of HF. Patients with higher NT-proBNP during admission experienced more frequent bleeding, arrhythmias and HF decompensations. NT-proBNP was associated with mortality both in the whole study population and after excluding patients with HF. A multivariable Cox model confirmed that NT-proBNP was independently associated with mortality after adjusting for all relevant confounders (hazard ratio 1.28, 95% confidence interval 1.13–1.44, per logarithmic unit).

Conclusion

NT-proBNP is frequently elevated in COVID-19. It is strongly and independently associated with mortality after adjusting for relevant confounders, including chronic HF and acute HF. Therefore, its use may improve early prognostic stratification in this condition.

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Graphical Abstract



NT-proBNP is frequently elevated in patients with COVID-19 and is strongly associated with myocardial injury and all-cause mortality.

Keywords

Natriuretic peptides • NT-proBNP • COVID-19 • Prognosis • Mortality • Heart failure

Introduction

Myocardial injury is a common complication in patients with coronavirus disease 2019 (COVID-19) and has been associated with poor outcomes. However, most researchers and definitions have focused on cardiac troponins and cardiac magnetic resonance imaging.^{1–4} Data regarding natriuretic peptides are scarce. B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) are quantitative plasma biomarkers usually reflecting haemodynamic cardiac stress and, therefore, play a central role in the diagnosis and management of heart failure (HF).⁵ In addition, they have shown optimal prognostic accuracy, as compared with complex multivariable risk scores,^{6–8} among patients with pulmonary embolism and pneumonia, both frequent complications after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Although COVID-19 has been associated with a wide spectrum of cardiovascular conditions (such as acute arterial thrombotic events, venous thromboembolic disease and arrhythmias),⁹ the potential association of these clinical events with natriuretic peptide elevation is not well defined. Furthermore, the identification of natriuretic peptides as a powerful independent predictor for prognostic stratification in COVID-19 patients would be ideal, given their wide availability and their potential to be assessed not only at hospital admission but also in the event of clinical deterioration during follow-up.

Thus, the primary aim of the present study was to investigate the association of NT-proBNP and mortality in a large cohort of consecutive patients with confirmed SARS-CoV-2 infection and a prolonged period of follow-up.

Methods

Study design and participants

We screened all consecutive patients with clinical suspicion of COVID-19 who attended the emergency room in a tertiary care centre in Madrid, Spain, from March 1st to April 20th, 2020. Patients were only included in the study if they had confirmation of SARS-CoV-2 infection by RNA reverse-transcriptase polymerase chain reaction (RT-PCR) assay and have at least one NT-proBNP determination after hospital admission. We aimed to include patients who have completed a follow-up of at least 30 days since their diagnosis. Therefore, patients who were alive and diagnosed less than 30 days before the lock of the database were excluded from the present analysis. This study was approved by our Institutional Review Board. Individual written informed consent was waived based on legal standards for national healthcare alarm situations.

Data collection

Epidemiological, demographic, clinical, laboratory, treatment, and outcome data were extracted from electronic medical records from the

index and subsequent hospital admissions using a standardized electronic data collection form. In addition, the central healthcare record system, which collects information and medical reports from all public hospitals and primary healthcare centres from the Madrid region was reviewed for additional follow-up data. All data were thoroughly reviewed by a team of 13 cardiologists. Any disagreements regarding data classification were reviewed by the whole team, and a decision was finally made by consensus. Special care was given to the identification of baseline cardiovascular profiles, clinical outcomes and specifically acute HF diagnosis.

Laboratory assays

Both the first and the peak determinations of NT-proBNP and troponin during hospital admission were investigated in the present analysis. NT-proBNP determinations were performed with a dedicated assay using chemiluminescence (Atellica Solution IM 1600, Siemens Healthineers, Erlangen, Germany), the limit of detection being 35 pg/mL, with an analytical imprecision of 5.3% at 160 pg/mL and 5.5% at 5476 pg/mL. Routine upper normal limits as defined by the local laboratory are <125 pg/mL for patients under 70 years and <450 pg/mL for patients over 70 years. Additionally, for the present analysis we systematically identified patients with abnormal NT-proBNP levels according to recommended cut-off values by the Heart Failure Association of the European Society of Cardiology (ESC): >450 pg/mL in patients below 50 years, >900 pg/mL in patients between 50–75 years, and >1800 pg/mL in patients over 75 years.⁶ Troponin determinations were performed with a dedicated troponin I assay using chemiluminescence (Atellica Solution IM 1600, Siemens Healthineers). According to the International Federation of Clinical Chemistry definition, this method is considered as a high-sensitivity troponin. The 99th percentile upper reference limit is 34.1 ng/L for males and 53.5 for females, the limit for detection being 2.6 ng/L. Analytical imprecision has been identified as 5.5% at 36.4 ng/L and 3.8% at 11 711 ng/L.

Study definitions

The primary endpoint of the present study was all-cause mortality. Thromboembolic events during follow-up were defined as the diagnosis of deep vein thrombosis, pulmonary embolism, stroke, or acute coronary syndrome based on appropriate imaging criteria. Major bleeding was defined as specified in the Thrombolysis in Myocardial Infarction (TIMI) bleeding classification¹⁰ (drop in haemoglobin ≥ 5 g/dL, intracranial or fatal bleeding). Chronic HF was defined as history of previous congestive decompensation or diagnosis of left ventricular systolic dysfunction (left ventricular ejection fraction <40%). Arrhythmias during admission were defined as new onset of atrial (atrial fibrillation/flutter) or ventricular (ventricular tachycardia/fibrillation) arrhythmias during follow-up. Acute HF refers to rapid onset or worsening of symptoms and/or signs of HF during the study period. Acknowledging the difficulty to distinguish between respiratory and cardiac causes of dyspnoea in COVID-19, acute HF events were adjudicated on a case-by-case basis by consensus of all investigators, as previously published.¹¹ We based our decisions on all clinical information available for each patient: codified HF diagnosis, description of serial physical examinations in the electronic medical records, radiological tests (chest radiography and computed tomography), available echocardiographic studies and the aforementioned NT-proBNP levels according to the recommended cut-off values of the Heart Failure Association of the ESC for the diagnosis of acute HF. We used the National Early Warning Score 2

(NEWS2) at the time of first NT-proBNP assessment, a standardized clinical scoring system developed to improve detection of deterioration in acutely ill patients, to further stratify the severity of COVID-19 cases in the study population.¹²

Statistical analysis

Categorical variables are shown as rates and percentages, and continuous variables as mean \pm standard deviation or median (interquartile range) as appropriate. Normality of distributions was assessed using Shapiro–Wilk test. Means for continuous variables were compared using independent group *t* tests when data were normally distributed, otherwise, Mann–Whitney test was performed. Proportions for categorical variables were compared using the χ^2 test or the Fisher exact test, as appropriate. For the analysis as a continuous variable, the first and the peak NT-proBNP and high-sensitivity troponin I (hs-TnI) concentrations assessed during the whole study period were log-transformed as a linearizing transformation. Survival during follow-up was assessed using Kaplan–Meier analysis and the log-rank test. The association of NT-proBNP with mortality was studied using Cox proportional-hazards models accounting for clinically relevant covariates (age, sex, cardiovascular risk factors, cardiac comorbidities, history of chronic kidney disease, vital signs at admission, NEWS2 score, treatment with corticosteroids and in-hospital complications). Subsequent adjustment with hs-TnI and D-dimer was additionally performed in those patients with available determinations of those biomarkers. All data were analysed using the Stata v14.2 statistics package (StataCorp, College Station, TX, USA). A two-sided *P*-value <0.05 was considered statistically significant for every analysis.

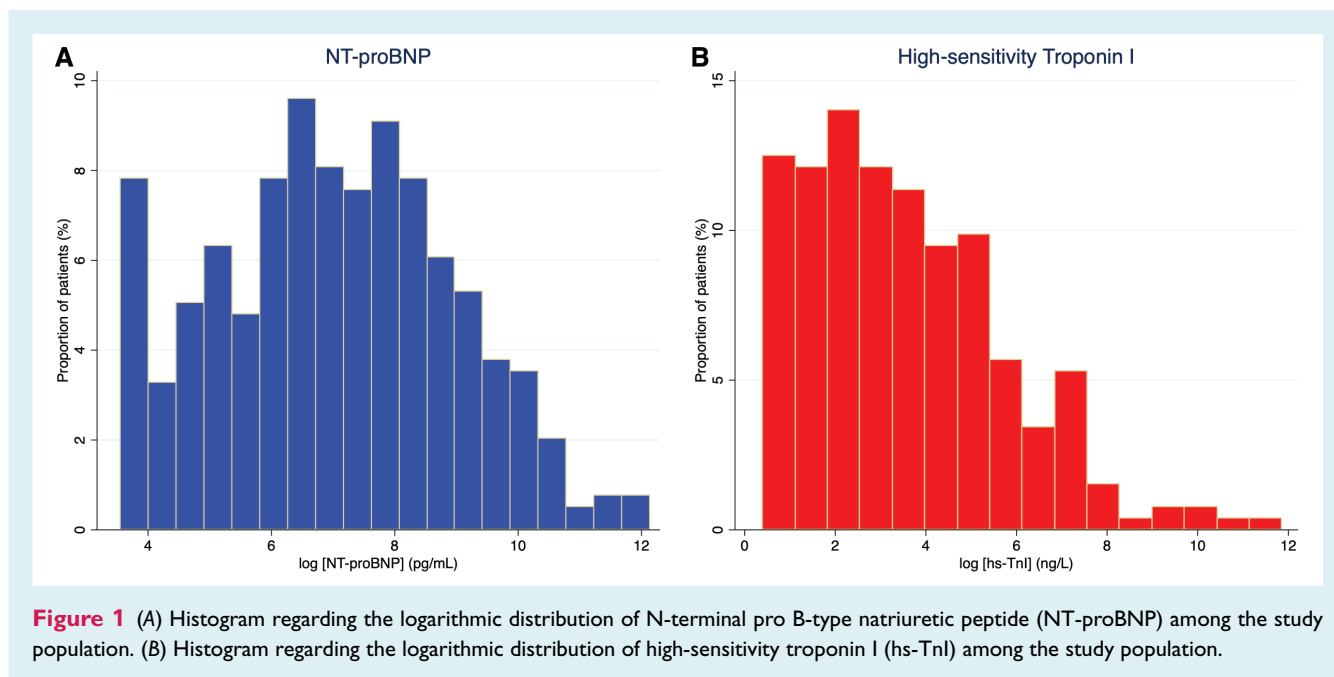
Results

Study patients

During the study period, 3080 consecutive patients with confirmed SARS-CoV-2 infection attended the emergency department of our tertiary care centre and were screened for participation in the present study (online supplementary Figure S1). Of these, 396 (mean age 71.8 ± 14.6 years, 61.1% male) fulfilled all the selection criteria and were ultimately included in the present analysis (differences between included and excluded patients are shown in online supplementary Table S1). The median follow-up was 53 (18–62) days, with the vast majority requiring hospital admission ($n = 376$, 95.0%), the leading reason being respiratory failure due to pneumonia ($n = 336$, of whom 263 had bilateral infiltrates).

NT-proBNP assessment

The median NT-proBNP at first determination was 847.5 (220.5–3625.5) pg/mL and the median peak NT-proBNP was 1047.0 (267.0–4648.5) pg/mL. Time since SARS-CoV-2 diagnosis to first NT-proBNP assessment was 4 days (0–10), while time since SARS-CoV-2 diagnosis to peak NT-proBNP was 5 days (1–13). Given that median time since diagnosis to death or medical discharge was 14 days (8–24), most first NT-proBNP determinations were performed during the early course of hospital admission. The distribution of the logarithmic NT-proBNP



concentration among participants is shown in *Figure 1A*. A total of 192 (48.5%) presented NT-proBNP levels above the recommended cut-off values for the identification of acute HF as recommended by the Heart Failure Association of the ESC.⁶ However, only 47 fulfilled clinical criteria for the diagnosis of HF, as previously defined.¹¹

The categorization of first NT-proBNP assessment during hospital admission (*Table 1*) illustrated that patients with higher level of natriuretic peptides were older, had more cardiac and non-cardiac comorbidities, presented poorer vital signs at the initial medical contact and had higher punctuation as assessed by the NEWS2 scoring system (*Figure 2A*). They also showed more profound abnormalities in troponin, D-dimer and coagulation assessments. On the other side, no statistical differences were identified regarding the time elapsed since the onset of symptoms, dedicated COVID-19 treatment (except for azithromycin) and inflammatory parameters such as C-reactive protein and fibrinogen. Patients with higher NT-proBNP showed higher all-cause mortality during follow-up. They also experienced more frequent HF decompensations and showed a non-significant trend towards new arrhythmic events during follow-up (*Table 2*). A complementary analysis of peak NT-proBNP levels during hospital admission showed similar results. However, peak NT-proBNP concentrations were significantly associated with higher C-reactive protein and higher incidence of major bleeding and cardiac arrhythmias (online supplementary *Tables S2* and *S3*).

Other cardiovascular biomarkers

Among the present study participants, hs-TnI was assessed in 264 patients, median time from SARS-CoV-2 diagnosis to peak hs-TnI being 6 (2–13) days. The distribution of the logarithmic hs-TnI concentration is displayed in *Figure 1B*. A total of 27 patients

(10.2%) presented hs-TnI levels below the limit of detection, 134 (50.8%) had measurable hs-TnI levels below the 99th upper reference limit and 103 (39.0%) fulfilled the criteria for myocardial injury as defined in the fourth universal definition of myocardial infarction.¹³ These categories were significantly associated with increasing NT-proBNP concentrations (*Table 1*; *Figure 2B*). On the other hand, a total of 358 patients underwent D-dimer assessment during hospital admission. D-dimer was found to be significantly increased through higher quartiles of NT-proBNP (*Table 1*; *Figure 2C*).

Mortality during follow-up

A total of 152 patients (38.4%) died during the study period. Time-to-event analysis confirmed that first NT-proBNP concentrations during hospital admission were significantly associated with mortality both in the whole study population (*Figure 3A*) and in the subgroup of patients who did not develop HF decompensations (*Figure 3B*) ($P < 0.001$ for both comparisons by the log-rank test). Hazard ratios (HR) and 95% confidence intervals are shown in online supplementary *Table S4*. A multivariable Cox proportional-hazards model (*Table 3*) confirmed that NT-proBNP concentration was independently associated with mortality after adjusting for all potentially relevant confounders [HR 1.28 (1.13–1.44) per logarithmic unit, $P < 0.001$]. Results were similar when peak NT-proBNP concentrations during admission were considered (online supplementary *Figure S2* and *Table S5*). Additionally, we performed complementary analyses in order to consider further adjustment for hs-TnI and D-dimer among the subgroup of patients in which these biomarkers were available (online supplementary *Tables S6* and *S7*). Even after adjusting for these relevant covariates, NT-proBNP remained independently associated with all-cause mortality during follow-up [HR

Table 1 Baseline characteristics according to the different quartiles of N-terminal pro B-type natriuretic peptide

	All patients (n = 396)	First quartile (n = 99)	Second quartile (n = 99)	Third quartile (n = 99)	Fourth quartile (n = 99)	P-value
Age (years)	71.8 ± 14.6	60.4 ± 14.7	71.8 ± 11.2	74.5 ± 13.2	80.4 ± 11.3	0.017
Male sex, n (%)	242 (61.1)	61 (61.6)	62 (62.6)	60 (60.6)	59 (59.6)	0.976
Time symptoms–diagnosis (days)	6.2 ± 4.9	6.5 ± 5.1	6.3 ± 4.4	6.3 ± 4.8	5.5 ± 5.5	0.184
Hypertension, n (%)	239 (60.4)	41 (41.4)	62 (62.6)	66 (66.7)	70 (70.7)	<0.001
Diabetes, n (%)	105 (26.5)	21 (21.2)	28 (28.3)	27 (27.3)	29 (29.3)	0.542
Dyslipidaemia, n (%)	199 (50.3)	41 (41.4)	48 (48.5)	51 (51.5)	59 (59.6)	0.037
Coronary heart disease, n (%)	49 (12.4)	6 (6.1)	10 (10.1)	13 (13.1)	20 (20.2)	0.017
Chronic heart failure, n (%)	44 (11.1)	1 (1.0)	4 (4.0)	13 (13.1)	26 (26.3)	<0.001
Atrial fibrillation, n (%)	58 (14.7)	0 (0.0)	2 (2.0)	21 (21.2)	35 (35.4)	<0.001
TIA/stroke, n (%)	40 (10.1)	2 (2.0)	5 (5.1)	12 (12.1)	21 (21.2)	0.001
CKD, n (%)	46 (11.6)	1 (1.0)	6 (6.1)	11 (11.1)	28 (28.3)	<0.001
PAD, n (%)	49 (12.4)	6 (6.1)	10 (10.1)	13 (13.1)	20 (20.2)	0.0019
COPD, n (%)	54 (13.6)	6 (6.1)	17 (17.2)	13 (13.1)	18 (18.2)	0.054
SBP at admission (mmHg)	129.3 ± 23.0	125.6 ± 18.2	129.1 ± 22.5	130.3 ± 22.5	131.5 ± 27.5	0.002
SaO ₂ at admission (%)	89.8 ± 8.2	91.1 ± 6.3	89.8 ± 7.8	89.2 ± 8.9	89.1 ± 9.9	<0.001
Supplementary O ₂ at admission, n (%)	69 (17.4)	9 (9.1)	20 (20.2)	24 (24.2)	16 (16.2)	0.024
Chest radiography at admission						0.324
No pneumonia	60 (15.2)	20 (20.2)	13 (13.1)	17 (17.2)	10 (10.1)	
Unilateral pneumonia	73 (18.4)	14 (14.1)	16 (16.2)	21 (21.2)	22 (22.2)	
Bilateral pneumonia	263 (66.4)	66 (65.7)	70 (70.7)	61 (61.6)	67 (67.7)	
NEWS2 score	5 (3–7)	4 (3–6)	5 (3–7)	6 (3–8)	6 (4–8)	<0.001
NT-proBNP (first), pg/mL	848 (221–3626)	96 (49–246)	462 (338–651)	1631 (1122–2407)	8437 (5018–18399)	<0.001
hs-TnI (max), ng/L	24.6 (6.4–140.0)	5.6 (2.5–26.4)	18.3 (7.9–89.6)	40.8 (12.3–131.7)	156.7 (49.8–735.9)	<0.001
CRP (max), mg/L	189.4 (103.5–282.3)	181.4 (57.3–278.9)	174.6 (103.8–257.1)	212.8 (111.3–303.9)	198.0 (113.6–280.3)	0.686
Fibrinogen (max), mg/dL	1030 (730–1200)	1034 (724–1200)	1028 (741–1200)	1141 (765–1200)	928 (642–1200)	0.283
Prothrombin act. (min)	71 (54–85)	79 (69–91)	75 (59–87)	66.5 (35–79)	63 (46–79)	<0.001
D-dimer (max), ng/mL	3541 (1143–15570)	3004 (830–10830)	3020 (1171–14010)	3368 (1143–15570)	4616 (1650–22451)	<0.001
Hydroxychloroquine, n (%)	359 (90.7)	88 (88.9)	92 (92.9)	90 (90.9)	89 (89.9)	0.791
Lopinavir/ritonavir, n (%)	59 (14.9)	15 (15.2)	15 (15.2)	14 (14.1)	15 (15.2)	0.996
Azithromycin, n (%)	236 (59.6)	67 (67.7)	65 (65.7)	59 (59.6)	45 (45.5)	0.006
Corticosteroids, n (%)	146 (36.9)	34 (34.3)	40 (40.4)	34 (34.3)	38 (38.4)	0.760
Remdesivir, n (%)	12 (3.0)	7 (7.1)	2 (2.0)	2 (2.0)	1 (1.0)	0.102

CKD, chronic kidney disease; COPD, chronic pulmonary obstructive disease; CRP, C-reactive protein; hs-TnI, high-sensitivity troponin I; NEWS2, National Early Warning Score 2; NT-proBNP, N-terminal pro B-type natriuretic peptide; PAD, peripheral arterial disease; SaO₂, oxygen saturation; SBP, systolic blood pressure; TIA, transient ischaemic attack.

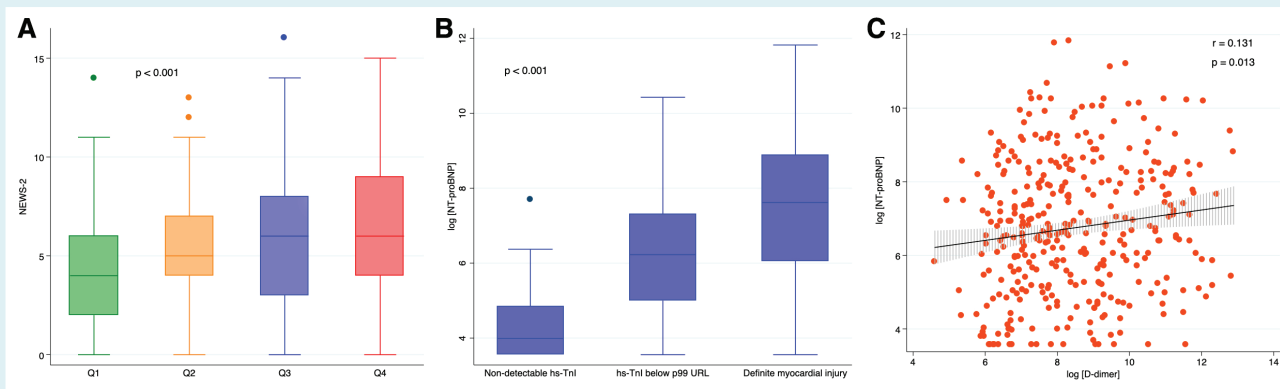


Figure 2 (A) Boxplot demonstrating the National Early Warning Score 2 (NEWS-2) score among quartiles of N-terminal pro B-type natriuretic peptide (NT-proBNP). (B) Boxplot showing NT-proBNP concentrations through different categories of high-sensitivity troponin I (hs-TnI). (C) Dot plot demonstrating a moderate correlation between the logarithmic concentrations of NT-proBNP and D-dimer ($P = 0.013$, correlation coefficient 0.131). URL, upper reference limit.

Table 2 Clinical outcomes according to the different quartiles of N-terminal pro B-type natriuretic peptide

Variable	All patients (n = 396)	First quartile (n = 99)	Second quartile (n = 99)	Third quartile (n = 99)	Fourth quartile (n = 99)	P-value
PE	38 (9.6)	13 (13.1)	10 (10.1)	8 (8.1)	7 (7.1)	0.512
DVT	9 (2.3)	2 (2.0)	3 (3.0)	4 (4.0)	0 (0.0)	0.262
ACS	2 (0.5)	0 (0.0)	0 (0.0)	2 (2.0)	0 (0.0)	0.248
TIA/stroke	3 (0.8)	1 (1.0)	1 (1.0)	1 (1.0)	0 (0.0)	1.000
PAD	7 (1.8)	1 (1.0)	2 (2.0)	2 (2.0)	2 (2.0)	1.000
Major bleeding	13 (3.3)	2 (2.0)	2 (2.0)	4 (4.0)	5 (5.1)	0.626
Arrhythmias	51 (12.9)	9 (9.1)	11 (11.1)	11 (11.1)	20 (20.2)	0.088
Heart failure	47 (11.9)	0 (0.0)	3 (3.0)	20 (20.2)	24 (24.2)	<0.001
Mechanical ventilation	91 (23.0)	23 (23.2)	25 (25.3)	26 (26.3)	17 (17.8)	0.382
ICU admission	95 (24.0)	25 (25.3)	25 (25.3)	27 (27.3)	18 (18.2)	0.442
Death	152 (38.4)	16 (16.2)	24 (24.4)	42 (42.4)	70 (70.7)	<0.001

Data are given as n (%).

ACS, acute coronary syndrome; DVT, deep vein thrombosis; ICU, intensive care unit; NT-proBNP, N-terminal pro B-type natriuretic peptide; PAD, peripheral arterial disease; PE, pulmonary embolism; TIA, transient ischaemic attack.

1.22 (1.03–1.45) and HR 1.23 (1.08–1.41) per logarithmic unit, respectively].

Discussion

The present study findings support the hypothesis that natriuretic peptides are highly associated with prognosis in COVID-19 patients (*Graphical Abstract*). Data regarding the role of NT-proBNP in this clinical condition mainly come from several small studies performed during the early stages of the pandemic.^{14–16} This preliminary research pointed out a potential relationship between NT-proBNP and worse outcomes but was limited by small sample sizes and poor characterization of the distribution of NT-proBNP concentrations. A recent meta-analysis including 13 observational studies and 2248 patients (most of them also from the early COVID-19 outbreak in China) also supported the

idea that NT-proBNP assessment may improve the discrimination of high-risk patients.¹⁷ However, this analysis only investigated mean NT-proBNP levels (while this biomarker typically presents a non-normal distribution) and had a high potential for confounding (as no multivariable analysis was performed).

Multiple pathophysiological pathways may be responsible for the elevation of NT-proBNP levels after SARS-CoV-2 infection. Inflammation by itself has been postulated as a possible driver for higher circulating natriuretic peptides¹⁸; however, the exact mechanism underlying this association is not yet fully understood. Interestingly, in our series inflammatory biomarkers such as C-reactive protein were not significantly associated with the first NT-proBNP determination after COVID-19 diagnosis. However, this relationship became significant at the time of peak NT-proBNP assessment during admission. Pneumonia and pulmonary embolism are both well-known complications of COVID-19^{19,20} and clinical

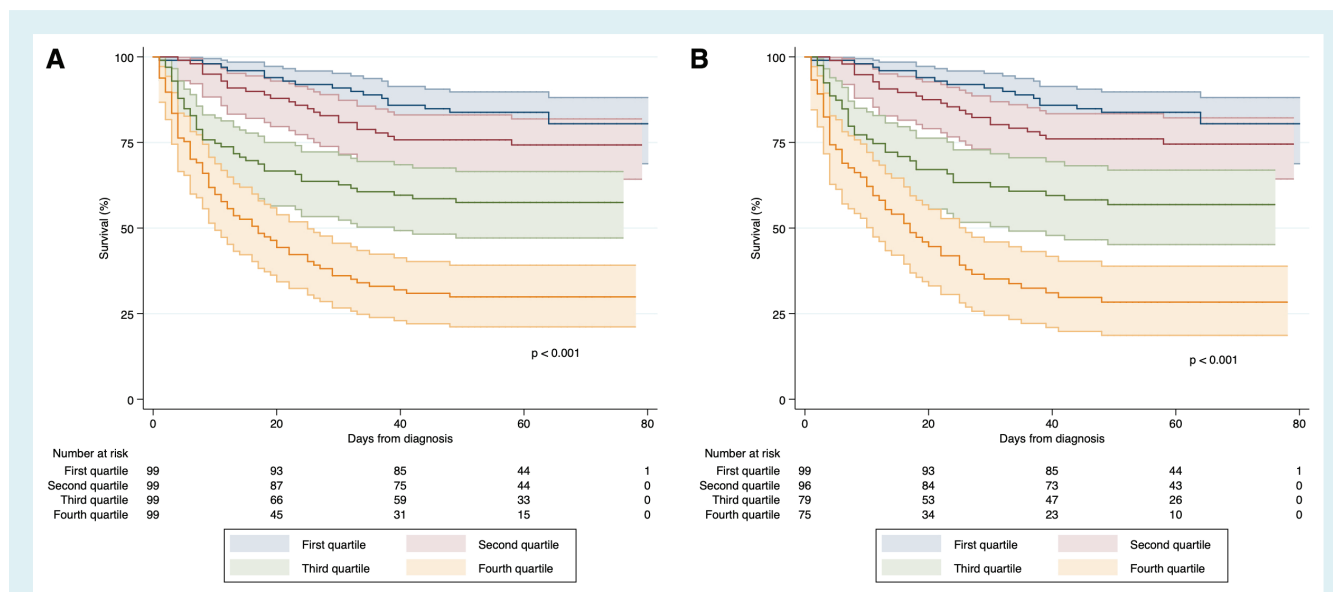


Figure 3 (A) Kaplan–Meier survival curves regarding all-cause mortality according to the quartiles of first N-terminal pro B-type natriuretic peptide (NT-proBNP) assessment in the whole study population. (B) Kaplan–Meier survival curves regarding all-cause mortality according to the quartiles of first NT-proBNP assessment excluding those patients who developed acute heart failure after SARS-CoV-2 infection.

Table 3 Cox proportional-hazards model assessing the relationship between N-terminal pro B-type natriuretic peptide and mortality during follow-up adjusted for multiple relevant covariates

Variable	Univariable			Multivariable		
	HR (95% CI)	SE	P-value	HR (95% CI)	SE	P-value
NT-proBNP (per log. unit)	1.47 (1.35–1.61)	0.07	<0.001	1.28 (1.13–1.44)	0.08	<0.001
Age (per 10 years)	1.54 (1.35–1.75)	0.10	<0.001	1.59 (1.33–1.91)	0.15	<0.001
Male sex	1.18 (0.85–1.66)	0.20	0.323	1.16 (0.80–1.69)	0.22	0.437
Hypertension	1.27 (0.91–1.76)	0.21	0.161	0.96 (0.65–1.40)	0.19	0.815
Diabetes	1.13 (0.79–1.61)	0.20	0.503	1.01 (0.68–1.51)	0.21	0.947
Dyslipidaemia	1.11 (0.80–1.53)	0.18	0.532	0.83 (0.56–1.23)	0.17	0.359
Atherosclerotic disease	1.75 (1.24–2.49)	0.31	0.002	1.54 (1.01–2.36)	0.33	0.046
Chronic kidney disease	1.74 (1.13–2.70)	0.39	0.013	1.01 (0.61–1.68)	0.26	0.959
Prior heart failure	1.33 (0.83–2.16)	0.33	0.240	0.79 (0.45–1.40)	0.23	0.420
Corticosteroids	1.39 (1.01–1.92)	0.23	0.042	1.09 (0.76–1.56)	0.20	0.623
SaO ₂ at admission (per 10%)	0.63 (0.54–0.72)	0.05	<0.001	0.68 (0.58–0.80)	0.05	<0.001
SBP at admission (per 10 mmHg)	0.95 (0.89–1.03)	0.04	0.212	1.00 (0.99–1.00)	0.00	0.409
NEWS2 score	1.20 (1.15–1.26)	0.03	<0.001	1.19 (1.12–1.27)	0.04	<0.001
Heart failure during admission	1.71 (1.11–2.65)	0.38	0.016	1.43 (0.89–2.31)	0.35	0.140
Mechanical ventilation	1.52 (1.08–2.13)	0.26	0.016	1.37 (0.85–2.20)	0.33	0.191

CI, confidence interval; HR, hazard ratio; NEWS2, National Early Warning Score 2; NT-proBNP, N-terminal pro B-type natriuretic peptide; SaO₂, oxygen saturation; SBP, systolic blood pressure; SE, standard error.

entities in which NT-proBNP has proven useful to improve prognostic stratification.^{7,8} Both situations may potentially result in right ventricular strain and higher intracavitary pressures in right cardiac chambers. Interestingly, we did not identify more extensive radiological pneumonia or higher incidence of pulmonary embolism among patients with higher NT-proBNP, and a recent study using right heart catheterization showed only mild

elevation of pulmonary artery pressure in ventilated patients with COVID-19.²¹

It has been postulated that the elevation of natriuretic peptides may be associated with concomitant impairment of cardiac function in COVID-19.^{3,22} According to the recommendations of international scientific societies including the ESC, the use of non-invasive imaging modalities was restricted and

generally limited to point-of-care ultrasound. Therefore, complete echocardiographic reports including the quantification of left ventricular systolic function were lacking for the majority of patients included in the present analysis. Nevertheless, our findings show that this association between NT-proBNP levels and mortality remains independent of the development of HF decompensations during hospital admission or the presence of chronic HF. This fact underscores that natriuretic peptides are not specific for the diagnosis of HF and careful clinical evaluation remains key for the assessment of patients with dyspnoea.^{5,6}

Besides, myocardial injury in COVID-19 (defined as the elevation of high-sensitivity troponin) has been the subject of extensive research. Potentially, it may result in increased wall stress and consequently higher NT-proBNP levels. Studies focused on cardiac magnetic resonance have suggested an elevated prevalence of myocardial inflammation among these patients. However, a recent international multicentre cardiac pathology study showed that, despite the frequent presence in cardiac samples of interstitial macrophages without clearly associated myocardial injury, only a minority of patients actually fulfilled the criteria for myocarditis.²³ Besides, direct damage to cardiac myocytes caused by SARS-CoV-2 may be less frequent than initially thought, but fibrin microthrombi in the cardiac microvasculature may play a significant role.²⁴ Other thrombotic complications with cardiac involvement, such as acute coronary syndromes,²⁵ and widespread alveolar capillary microthrombi²⁶ have been described. These situations may be mediated by dysregulated immunothrombosis, a condition that has been linked to systemic hypercoagulability and acute respiratory distress in COVID-19.²⁷ Our findings are consistent with the hypothesis of the development of myocardial injury and microvascular thrombosis being related to high wall stress and increased NT-proBNP levels. However, we were not able to identify a predominant mechanism for myocardial injury and the majority of cases may be explained by a multifactorial origin.

Prognostic stratification has remained a recurrent challenge in the management of COVID-19 and multiple prognostic models have been developed to support medical decision making. However, significant methodological limitations have been pointed out²⁸ and, after systematic evaluation, no single prognostic model has shown incremental value for risk stratification over several individual predictors such as age and oxygen saturation.²⁹ Standard clinical scoring systems such as the NEWS2 score may play a certain role. However, data from large cohorts have suggested that they may have poor discrimination, also showing that risk stratification may be improved after the inclusion of specific biomarkers.³⁰ Based on the present study findings and its wide availability, we believe that the addition of NT-proBNP to the initial assessment of COVID-19 patients may improve prognostic stratification at first medical contact. Ongoing research regarding COVID-19 prognostication should include NT-proBNP as a variable of interest to predict disease outcomes.

Limitations

This is an observational, retrospective, single-centre study with the inherent limitations of this type of design (i.e. the impossibility of

establishing definitive causal associations). Besides, it may be possible that prioritization of hospital resources and isolation protocols to avoid the spread of the disease may have led to restricted computed tomography for the diagnosis of pulmonary embolism. This may have resulted in underestimation of thromboembolic events during follow-up. On the other hand, NT-proBNP was not routinely assessed in every patient after the diagnosis of SARS-CoV-2 infection and that fact may have introduced a certain selection bias: patients included in the present analysis were older, had more comorbidities and ultimately underwent much more frequent hospitalization than those who did not undergo natriuretic peptide assessment. Thus, our sample should not be viewed as representative of the whole COVID-19 population as it barely included mild patients who can be managed in an ambulatory setting. Although this fact limits the generalizability of the results, we believe that our findings are useful and valuable for physicians attending moderate or severe COVID-19 patients who undergo hospital admission.

Conclusion

In this large cohort of consecutive patients with confirmed SARS-CoV-2 infection, NT-proBNP levels were frequently elevated, with a large proportion of patients showing concentrations well above the suggested cut-off for the diagnosis of HF according to the ESC Heart Failure Association. However, only a minority of patients fulfilled the clinical criteria for the diagnosis of HF. A multivariable Cox proportional-hazards model showed that NT-proBNP was independently associated with mortality after adjusting for all relevant confounders. This relationship was independent of the development of HF decompensations during hospital admission, the presence of chronic HF and the elevation of other relevant biomarkers such as troponin and D-dimer.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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