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Review

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Abstract

NT-proBNP is a peptide related to brain natriuretic peptide, a cardiac biomarker and a member of the natriuretic family of peptides. NT-proBNP has demonstrated its clinical utility in the assessment of a wide spectrum of cardiac manifestations. It is also considered a more precise diagnostic and prognostic cardiac biomarker than brain natriuretic peptide. With the appearance of the Severe Acute Respiratory Syndrome Coronavirus 2 virus and the subsequent COVID-19 pandemic, diagnosis of heart implications began to pose an increasing struggle for the physician. Echocardiography is considered a central means of evaluating cardiac disorders like heart failure, and it is considered a reliable method. However, other diagnostic methods are currently being explored, one of which involves the assessment of NT-proBNP levels. In the literature that involves the adult population, significant positive correlations were drawn between the levels of NT-proBNP and COVID-19 outcomes such as high severity and fatality. In the paediatric population, however, the literature is scarce, and most of the investigations assess NT-proBNP in the context of Multiple Inflammatory Syndrome in Children, where studies have shown that cohorts with this syndrome had elevated levels of NT-proBNP when compared to non-syndromic cohorts. Thus, more large-scale studies on existing COVID-19 data should be carried out in the paediatric population to further understand the prognostic and diagnostic roles of NT-proBNP.

Introduction

In 1980, Adolfo de Bold and his colleagues provided a pertinent description of an endocrine activity that resulted from the cardiac atria of rats, and they associated this activity with the hormone “atrial natriuretic factor.”¹ This factor was then classified as the first member of the natriuretic peptide family and named atrial natriuretic peptide.² Currently, it has a well-recognized involvement in natriuresis, blood pressure regulation, electrolyte homeostasis, and so on.^{3,4} A couple of years later, Sudoh et al. reported a novel peptide with remarkable similarity to atrial natriuretic peptide but had distinguishable features. This protein was identified as the “porcine brain natriuretic peptide,” because it was isolated from the acid extracts of a pig brain.⁵ However, it was later isolated from rat, pig, and human hearts. Further studies showed that this new peptide is predominantly synthesised and released from the left ventricular chamber.^{6–8} It constituted the second member of the natriuretic peptide family and was renamed the “brain natriuretic peptide.” A molecule related to the brain natriuretic peptide is a 76-amino acid N-terminal peptide termed NT-proBNP, and this peptide has proved its clinical usefulness in the diagnosis of acute respiratory distress syndrome,⁹ and more commonly, heart failure.^{9–13} The clinical applications of NT-proBNP have long been utilised prior to COVID-19, and they not only include determining the severity of heart failure but also the risk stratification in patients with coronary artery disorders.¹⁴

The COVID-19 pandemic was the main source of considerable morbidity and mortality as of December 2019, and as a result, the worldwide community has faced and is still facing significant financial, social, and medical challenges.¹⁵ This pandemic is considered the third outbreak caused by the β -coronavirus family, following the Severe Acute Respiratory Syndrome in 2002 and the Middle East Respiratory Syndrome in 2012.¹⁶ Interestingly, evidence linking brain natriuretic peptide and NT-proBNP with the COVID-19 disease has surged, with multiple studies showing that the levels could be indicative of the severity of the disease.^{17–20} The relationship between brain natriuretic peptide/NT-proBNP and in-hospital mortality due to COVID-19 has also been tackled, with some studies correlating the high biomarker levels with a higher risk of mortality.^{21–24} Despite the existence of some studies on the paediatric population, larger systematic studies need to be carried out to yield a considerable body of evidence. The purpose of this review is to add evidence to the correlation of NT-proBNP with

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COVID-19 cardiovascular outcomes, with a special emphasis on the paediatric COVID-19 population.

Biochemical characteristics

Structure and synthesis

The NT-proBNP molecule traces its origins to a parent prohormone called proBNP, which is secreted by cardiomyocytes as a response to stress, cardiac pressure, or ventricular expansion^{25,26} Additional causes like myocardial ischaemia and endocrine or paracrine interference by other hormones and cytokines trigger the release of proBNP²⁷ This glycosylated prohormone is comprised of 108 amino acids, and it is subsequently de-glycosylated and cleaved by the proNP convertases (corin and furin) into the inactive 76-amino acid NT-proBNP and an active 32-amino acid C-terminal brain natriuretic peptide.^{28,29}

The human gene encoding brain natriuretic peptide is localised on the p arm of chromosome 1, and the messenger RNA encoding brain natriuretic peptide contains a repeat Thymine-Adenine-Thymine-Thymine-Thymine-Adenine-Thymine sequence that is considered unstable^{30,31} The data suggest that brain natriuretic peptide is regulated by post-translational processing, meaning that its gene product can rapidly increase when under proper stimuli^{32,33} The transcription of brain natriuretic peptide messenger RNA and the synthesis and secretion of the brain natriuretic peptide protein take place in an eruptive manner, where they are quickly released into surrounding tissues instead of being stored in the normal physiological cardiac tissue³¹ In pathological conditions, this unstable messenger RNA synthesises a pre-proBNP precursor composed of 134 amino acids, which once released into circulation, is further split into a signal peptide made up of 26 amino acids, and the 108 amino acid proBNP, which subsequently yields NT-proBNP, as can be seen in Figure 1.^{34-36,37}

Degradation and clearance

The three known natriuretic peptide receptors in mammals are natriuretic peptide receptor-A, natriuretic peptide receptor-B, and natriuretic peptide receptor-C, and the first two represent two of the five transmembrane guanylyl cyclases found in humans⁴⁰ Natriuretic peptide receptor-A is a receptor for both atrial natriuretic peptide and brain natriuretic peptide, and it is abundant in the vascular endothelial system, in addition to the brain, kidneys, adrenal glands, and lungs^{32,41} Natriuretic peptide receptor-B is a receptor for the third member of the natriuretic peptide family, the C-type natriuretic peptide, which aids in lowering blood pressure and in preventing the development of atherogenesis and aneurysms⁴² The third receptor, natriuretic peptide receptor-C, is also known as the clearance receptor, and its primary function is to clear circulating natriuretic peptides via receptor-mediated internalisation and degradation^{43,44,45} Of note is that natriuretic peptides can also be cleared by neutral endopeptidase, insulin-degrading enzyme, dipeptidyl peptidase-4, or renal excretion.⁴⁶

Since NT-proBNP is not an active natriuretic peptide, it cannot be cleared by natriuretic peptide receptor-C. Data have shown that there was no difference in plasma NT-proBNP levels between the aortic root and the peripheral veins, which means that this biomarker is not cleared in the systemic circulation⁴⁷ Studies have also shown that it is mainly cleared by the kidneys,⁴⁸⁻⁵⁰ and this means that renal dysfunction could potentially lead to the elevation of plasma NT-proBNP. In addition, studies have demonstrated

that impaired glomerular filtration and renal clearance in diseases like chronic kidney disease can cause the accumulation of NT-proBNP^{47,51} However, in patients with mild renal impairment, there seems to be no significant correlation between the glomerular filtration rate and the plasma levels of NT-proBNP,⁵² which opens the door for the possibility of other modes of clearance for NT-proBNP.

Correlation with cardiac function

Heart failure is considered a manifestation of the advanced stages of various cardiovascular diseases, including coronary artery disease, hypertension, valvular disease, and primary myocardial disease⁵³ Since increased cardiac wall stress is a common factor of many cardiac diseases, it follows that circulating NT-proBNP and brain natriuretic peptide can serve as clinical biomarkers of these disorders⁵⁴ While both peptides had an excellent ability to distinguish heart failure from non-heart failure subjects, it was shown that NT-proBNP was more sensitive and accurate⁵⁵ This may have to do with its higher stability at room temperature (for ethylenediaminetetraacetic acid assays for example)⁵⁶ and the fact that the half-life of serum NT-proBNP is around 120 mins, which is six times the mere 20 minutes of circulating brain natriuretic peptide, despite both molecules being released in equimolar concentrations.^{27,57} In a study by Emdin *et al.*, it was shown that both brain natriuretic peptide and NT-proBNP enabled the identification of asymptomatic patients at a risk of developing heart failure. Remarkably, NT-proBNP showed a higher precision for identifying mild heart failure,⁵⁸ making it a better diagnostic marker of heart failure than brain natriuretic peptide. It is commonly considered a gold standard biomarker in the prognosis of heart failure conditions such as chronic heart failure with reduced ejection fraction.^{59,60}

In the Acute Decompensated Heart Failure National Registry, admission NT-proBNP levels greater than 986 pg/ml were associated with an almost three-fold increase in one-year mortality⁶¹ In general, NT-proBNP levels that could be indicative of heart failure vary between age groups. According to the Heart Failure Association of the European Society of Cardiology, normal levels of NT-proBNP should be below 450 pg/ml in adult patients below 50 years, and below 900 pg/ml in patients between 50 and 75 years.⁶² As for the paediatric population, a study by Lin *et al.* showed that levels above approximately 600 pg/ml could be indicative of heart failure⁶³ (the Ross criteria are also needed for an accurate diagnosis). In another study, it was reported that the median NT-proBNP reference value in children aged zero to ten years, ten to thirteen years, and thirteen to eighteen years was 173.6, 118.5, and 61.1 pg/mL, respectively⁶⁴ As for neonates exclusively, they can have NT-proBNP levels in the order of thousands under normal conditions, with one study ranging the normal value from 250 pg/ml to 3,987 pg/ml⁶⁵ NT-proBNP levels tend to be very elevated in the first few days after birth, but their levels decrease and remain relatively constant throughout childhood, and they tend to plummet rapidly with advancing pubertal stages.^{66,67}

The NYHA Functional Classification has served as a fundamental tool for the stratification of heart failure classes despite some difficulties in its application.^{60,68} Indeed, many clinical studies uncovered a correlation between the NYHA classification and NT-proBNP levels, such that high levels of NT-proBNP indicate an unfavourable medium-term prognosis, while very low levels are associated with an excellent prognosis.⁶⁰

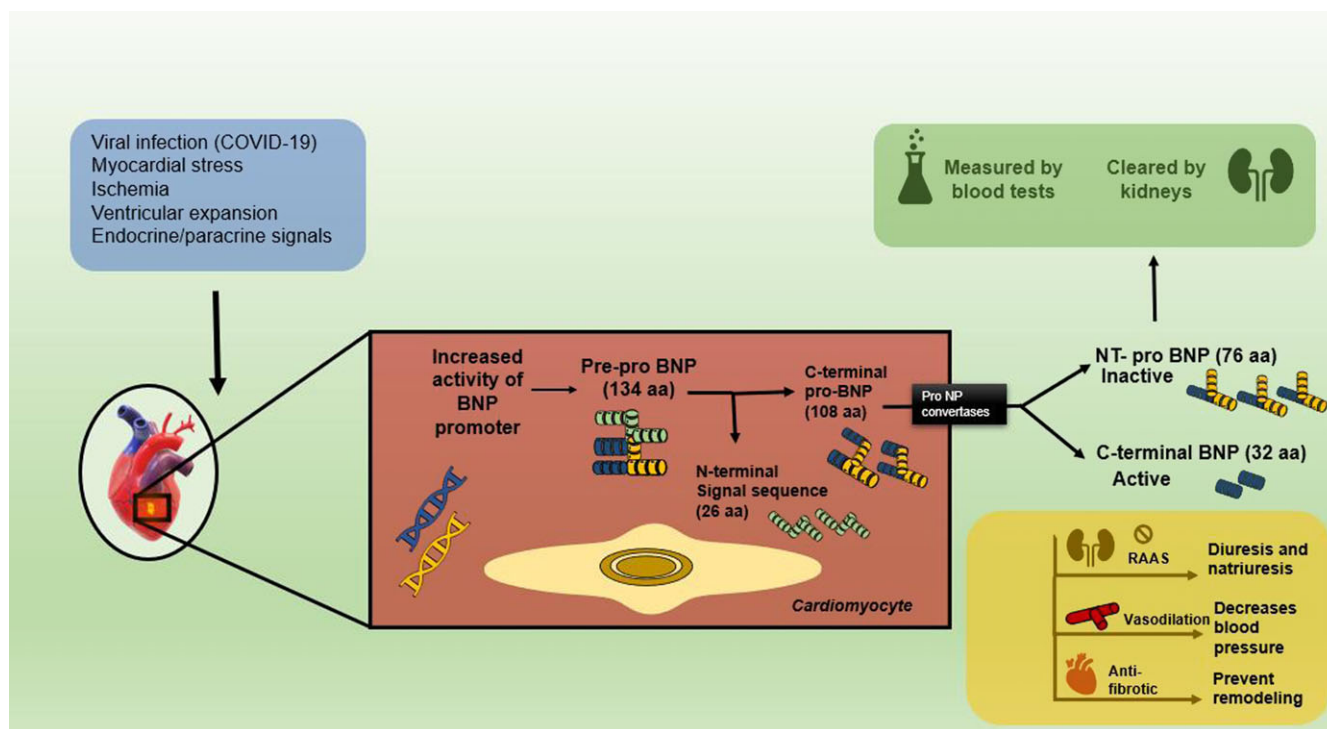


Figure 1. The pathways of brain natriuretic peptide and NT-proBNP synthesis. Represented are the aetiologies of the increased synthesis of pre-proBNP and the subsequent cleavage of its signal sequence to yield a C-terminal proBNP that also gets cleaved into the inactive NT-proBNP measured by blood tests and bioactive brain natriuretic peptide that plays a crucial role in maintaining homeostasis by performing the functions listed above.

In infants, NT-proBNP is becoming increasingly recognised as a potential screening tool for heart conditions like patent ductus arteriosus,⁶⁹ which, if left untreated, may lead to congestive heart failure and death.⁷⁰ However, no study has shown that NT-proBNP could be the sole diagnostic biomarker of a potential heart failure, and many have shown that it constitutes a supplement to echocardiography, not a replacement.^{71–73} Echocardiography still plays a central role in the diagnosis and evaluation of heart failure,^{74,75} and it is clearly essential in the evaluation of patients with heart failure with preserved ejection fraction, in terms of both diagnosis and prognosis.⁷⁶ As for the relationship between heart failure with preserved ejection fraction and heart failure with reduced ejection fraction with NT-proBNP, a study by Salah et al. demonstrated that patients with these two conditions have the same relative risk of 6-month death predicted by absolute discharge NT-proBNP levels or by percentage changes in NT-proBNP.⁷⁷

NT-proBNP in paediatrics

In the paediatric population, NT-proBNP levels were historically associated with multiple manifestations that were for the most cardiac.⁶⁶ Of the conditions we will encounter in the analyses of the different studies, the most common are Multisystem Inflammatory Syndrome in Children, Kawasaki Disease, cardiogenic shock, or even coronary artery abnormalities.^{78,79} Multisystem Inflammatory Syndrome in Children is an inflammatory condition that targets multiple systems, some of which are the nervous, gastrointestinal, integumentary, and cardiovascular.^{80,81} These symptoms are shared with a similar but still

distinct condition, Kawasaki Disease, where we also encounter instances of vasculitis and myocarditis in addition to the discussed “multi-organ” presentations.^{79,81,82} In some instances, coronary abnormalities and cardiogenic shock can present following either Kawasaki Disease or Multisystem Inflammatory Syndrome in Children, where coronary artery aneurysm and dilatation were observed for the former.^{78,83,84} Cardiogenic shock is a condition of poor cardiac efficiency in which the cardiac output is severely reduced, whether due to arrhythmias, instances of myocarditis, or ventricular dysfunction.⁸⁵ In a study by Lemm et al., NT-proBNP levels were elevated in patients with cardiogenic shock, which may have been heavily dependent on impaired renal function, suggesting and reflecting additional organ dysfunction.⁸⁶ In short, the data suggest a recurrent theme of multi-organ presentations, especially cardiac ones, when it comes to elevated NT-proBNP levels.

NT-proBNP and COVID-19

COVID-19 was deemed a global pandemic by the World Health Organization on March 11, 2020, due to its exponential global spread.^{87,88} Disease severity and mortality varied between populations, with patients having chronic cardiovascular diseases being some of the most heavily affected.⁸⁹ The Severe Acute Respiratory Syndrome Coronavirus 2 virus is known to down-regulate the expression of angiotensin-converting enzyme 2 receptor,^{90,91} and this consequently enhances the levels of circulating angiotensin II from cardiomyocytes.⁹² Unlike anti-inflammatory angiotensin 1-7, which is the derivative of angiotensin II,⁹³ angiotensin II is pro-inflammatory and facilitates

the secretion of NT-proBNP.⁹⁴ However, the linkage between the virus and NT-proBNP is still not fully elucidated. Evidence shows that Acute Respiratory Distress Syndrome induces right heart strain, ischaemia, hypoxaemia, and the previously mentioned inflammation, all of which can be stimulated directly or indirectly by the virus, notwithstanding the fact that not all of them increase heart wall stress.⁹⁵ Notably, the use of vasopressor therapy and hypoxia-induced pulmonary vasoconstriction has been shown to increase NT-proBNP levels.⁹⁶ In addition, as mentioned previously, renal dysfunction is among the non-cardiac causes of NT-proBNP elevation. This was also proven in the case of COVID-19 patients with acute and chronic kidney conditions.^{97,98}

With the relationship between COVID-19 and cardiovascular outcomes already established in the literature, it becomes evident that the NT-proBNP biomarker can be monitored for various COVID-19 cohorts, and ultimately tied with cardiovascular outcomes. The COVID-19 disease has devastated the entire world. Monitoring and early detection of the complications secondary to the viral infection became a top priority for the healthcare sector. Over the course of this pandemic, a lot of investigations pertaining to adult NT-proBNP levels were published. The bulk of studies focused on comparing severe versus non-severe COVID-19 cohorts, and on the more extreme end, survivor versus non-survivor COVID-19 cohorts. A 2020 study by He et al. reinforces the idea that NT-proBNP levels are indeed associated with disease severity given that the median of the severe COVID-19 cohort was 498 pg/ml, whereas that of the non-severe group was 21 pg/ml.²⁰ Other studies that reached a similar outcome are depicted in Table 1. None of the studies in Table 1 administered an echocardiography test, so we cannot rule out cardiac involvement and claim that the virus independently led to the abnormal rise in NT-proBNP levels, especially since this biomarker is a cardiac one after all.

In the adult population

As for the studies regarding adult mortality, they all converged on the fact that the cohort of deceased persons had higher levels of NT-proBNP when compared to those who survived the disease, as listed in Table 2. NT-proBNP levels are determined by a variety of different immunoassays that employ antibodies directed to distinct epitopes, and such assays notably include the Elecsys proBNP II and the Superflex NT-proBNP assays.⁹⁹ A study by Ferrari et al. depicted the highest mean (6,295.8 pg/ml) recorded in the deceased group, with an equally high standard deviation (17,527.6).¹⁰⁰ Almost all of the remaining studies found mean/median NT-proBNP levels in the order of thousands in the deceased group, but not one of them found this result in the non-deceased cohort, which fortifies the association between NT-proBNP levels and mortality post-COVID-19 incidence. Furthermore, five studies¹⁰¹⁻¹⁰⁵ administered an echocardiography test, and some of the parameters assessed were left ventricular ejection fraction, tricuspid annulus plane systolic excursion, pulmonary artery systolic pressure, right ventricular dilation, and several left ventricle variables.

In the study by D'Alto et al.,¹⁰¹ early and pronounced right ventricular arterial uncoupling was revealed by trans-thoracic echocardiography. The tricuspid annulus plane systolic excursion/pulmonary artery systolic pressure ratio also aided in clarifying the prognostic relevance of an indicator for lung severity (arterial partial pressure of oxygen/fraction of inspired O₂). In the same study, NT-proBNP levels were significantly increased in the

Table 1. Study characteristics and baseline NT-proBNP levels in adult severe versus non-severe COVID-19 cohorts

Reference	Authors	Year published	Study Type	Country	Number of Cases		% Male		Age		NT-proBNP level (pg/ml)		Other cardiac parameters assessed
					S	NS	S	NS	S	NS	S	NS	
18	Han et al.	2020	Retrospective	China	60	198	35.0	35.9	58.97 ± 14.38	58.95 ± 10.80	290.85 (106.13-958.98)	113.65 (45.92-274.23)	CK-MB, MYO, cTnI
112	Zhu et al.	2020	Retrospective	China	16	111	56.3	65.8	57.50 ± 11.70	49.95 ± 15.52	196.45 (75.85-405.10)	118.00 (78.38-218.75)	cTnI
113	Tao et al.	2021	Retrospective	China	20	202	40.0	35.6	65 (57-81)	54 (41-66)	524 (31.3-1876.5)	88 (15-489.8)	CK-MB, MYO, LDH
114	Yang et al.	2020	Retrospective	China	4	99	0.0	49.5	63.75 ± 9.67	441 ± 4.62	170.40 ± 0.00	1,705.28 ± 2,326.45	CK, CK-MB, cTnI
115	Zheng et al.	2020	Retrospective	China	32	67	59.4	47.8	63.81 ± 16.51	42.51 ± 15.11	1,085.55 ± 3217.11	66.92 ± 90.85	CK-MB, MYO, Hs-TnT
116	Lu et al.	2020	Retrospective	China	22	243	NA	NA	NA	NA	76.1 (37.7-694.0)	32.90 (22.4-61.0)	CK, MYO, LDH, Hs-TnT
20	He et al.	2020	Not mentioned	China	21	32	61.9	68.2	42	42	498 (241-1,726)	21 (8-97)	CK, CK-MB, cTnI, LDH
17	Abdeladim et al.	2020	Retrospective	Morocco	17	39	30.4	44.6	56.65 ± 16.85	49.59 ± 18.81	124.18 (72.27-176.08)	80.74 (46.66-114.83)	LDH, cTnI

S = severe; NS = non-severe; CK = creatine kinase; CK-MB = creatine kinase isoenzyme-MB; MYO = myoglobin; cTnI = cardiac troponin I; LDH = lactate dehydrogenase; Hs-TnT = high-sensitivity troponin T; Data are reported as N, or median (interquartile ranges), or mean ± standard deviation when appropriate. Some studies included a third group (signifying a more critical case than "severe," but the results of this group were excluded from the table above to maintain homogeneity between the studies).

Table 2. Study characteristics and baseline NT-proBNP levels in adult alive versus deceased COVID-19 cohorts

Reference	Authors	Year published	Study Type	Country	Number of Cases		% Male		Age		NT-proBNP level (pg/ml)		Other cardiac parameters assessed
					A	D	A	D	A	D	A	D	
¹⁰¹	D'Alto et al.	2020	Prospective	Italy	69	25	76.8	68.0	62 ± 13	68 ± 12	686 ± 1,224	3,375 ± 3,891	cTnI
¹¹⁷	Ciceri et al.	2020	Not mentioned	Italy	291	95	71.1	73.7	62 (54–72)	76 (67–82)	150 (60–409)	1,150 (331–3,268)	LDH, cardiac troponin
¹⁰⁰	Ferrari et al.	2020	Retrospective	Italy	40	42	67.5	71.4	60.4 ± 11.2	74.1 ± 11.3	690.2 ± 1,075.4	6,295.8 ± 17,527.6	LDH
¹⁰²	Rath et al.	2020	Prospective	Germany	107	16	60.7	75.0	67 ± 15	73 ± 16	377 (132–1,914)	1,992 (416–7,719)	CK, cTnI, LDH
¹¹⁸	Lorente et al.	2020	Prospective	Spain	118	25	44.9	28.0	64 (55–72)	71 (68–75)	288 (130–1,195)	3,480 (468–6,162)	LDH
¹¹⁹	Belarte-Tornero et al.	2021	Not mentioned	Spain	82	47	54.9	38.3	77.4 ± 13.7	85.5 ± 5.5	482 (180–893)	3,786 (1,391–10,400)	LDH, Hs-TnT
⁹⁶	Selçuk et al.	2021	Retrospective	Turkey	111	26	49.5	65.4	55 ± 14	66 ± 14	104 ± 140	845 ± 573	cTnI
¹²⁰	Yu et al.	2020	Retrospective	China	123	18	37.4	61.1	80.0 (77.0–85.0)	83.5 (80.8–86.3)	260.0 (124.0–512.0)	2,362.5 (1,707.6–2,978.3)	CK, CK-MB, cTnI, LDH
¹⁰³	Liu et al.	2020	Prospective	China	21	22	33.3	68.2	64.1 ± 9.8	64.9 ± 10.4	908.0 (580.0–4,088.0)	5804.0 (2,439.8–14,347.8)	Hs-cTnI
¹⁰⁴	Sun et al.	2020	Retrospective	China	123	121	41.5	67.8	67 (64–72)	72 (66–78)	174 (75–360)	824 (350–2,568)	Hs-cTnI
¹⁰⁵	Zhang et al.	2020	Retrospective	China	62	36	56.4	63.9	60.0 ± 1.9	70.5 ± 1.7	184 (75–671)	1,573 (542–7,487)	Hs-cTnI, LDH
¹²¹	Chen et al.	2020	Retrospective	China	53	20	50.9	75.0	64 (56.00–71.30)	69 (64.00–76.50)	301 (153–555)	794 (256–1,467)	Hs-cTnI, CK, LDH
¹²²	Deng et al.	2020	Retrospective	China	212	52	45.8	63.5	62.5 (52.0–70.0)	74.5 (65.3–81.8)	155.0 (64.4–460.3)	943.2 (402.3–2,397.5)	CK, CK-MB, MYO, cTnI-ultra, LDH

A = alive; D = deceased; CK = creatine kinase; CK-MB = creatine kinase isoenzyme-MB; MYO = myoglobin; cTnI = cardiac troponin I; LDH = lactate dehydrogenase; Hs-TnT = high-sensitivity troponin T; Hs-TnI = high-sensitivity troponin I. Data are reported as N, or median (interquartile ranges), or mean ± standard deviation when appropriate.

deceased cohort when compared to the survivors, as per Table 2. In another study by Rath *et al.*,¹⁰² trans-thoracic echocardiography revealed a significantly better left ventricular function in the survivors when compared to the non-survivors, and the NT-proBNP level was significantly lower in the survivors. As for Liu *et al.*¹⁰³ and Sun *et al.*,¹⁰⁴ a significant difference arose when comparing tricuspid annulus plane systolic excursion values between the alive and dead cohorts. The same applies when it comes to the NT-proBNP levels. We can therefore notice that there are significant correlations between some cardiac parameters (obtained from echocardiography) and survivorship. Similarly, significant correlations were evident when comparing NT-proBNP levels between the two groups. Therefore, direct associations between NT-proBNP and some echocardiographic parameters should be assessed for future research.

In the paediatric population

Until now, the NT-proBNP studies discussed were mainly focused on adult severe versus non-severe COVID-19 cohorts and deceased versus non-deceased COVID-19 cohorts. However, the literature also depicts novel findings about the value of NT-proBNP in the paediatric population affected by COVID-19, as shown in Table 3. In most studies dealing with paediatric COVID-19 patients, the main comparison groups established were Multisystem Inflammatory Syndrome in Children versus non-CMultisystem Inflammatory Syndrome in Children patients. In short, Multisystem Inflammatory Syndrome in Children, sometimes referred to as Pediatric Inflammatory Multisystem Syndrome is a complication that can follow a COVID-19 infection.⁸⁰ Clinically, it appears as a severe condition with specific features such as the inflammation of several systems.⁸⁰ However, cardiac dysfunctions are more commonly observed in Multisystem Inflammatory Syndrome in Children patients.^{80,106} A study by Wu and Campbell¹⁰⁶ indicates that cardiac manifestations may be present in up to 80% of paediatric patients diagnosed with Multisystem Inflammatory Syndrome in Children. Based on multiple sources of the literature, increased NT-proBNP concentrations are indeed associated with disease severity. In fact, most of the studies showed that children in the Multisystem Inflammatory Syndrome in Children group had significantly greater levels of circulating NT-proBNP compared to those in the non-Multisystem Inflammatory Syndrome in Children cohort (Table 3). A retrospective study led by Abrams *et al.*⁷⁸ further strengthens the discussed correlation, given that they divided 1,080 Multisystem Inflammatory Syndrome in Children patients into three groups: patients admitted to the ICU (on the same day of hospitalisation versus days after hospitalisation) and patients not admitted to the ICU. The median NT-proBNP level of the first cohort (admitted to the ICU on the same day) was 4,796 pg/ml, significantly greater than that of the third group (patients not admitted to the ICU) which was 558 pg/ml.⁷⁸ These results are crucial, as they indicate that patients requiring critical care during hospitalisation had great elevations of NT-proBNP, where the median was in the order of thousands. Other studies in Table 3 also point to similar findings, where Multisystem Inflammatory Syndrome in Children patients requiring intensive care had higher levels of NT-proBNP than those who did not ($p < 0.05$).^{107–110} It is important to note that Multisystem Inflammatory Syndrome in Children must be temporally associated with a Severe Acute Respiratory Syndrome Coronavirus 2 infection and is considered a post-infectious condition.⁸⁰ One study showed that children diagnosed with Multisystem Inflammatory Syndrome

in Children without evidence of a Severe Acute Respiratory Syndrome Coronavirus 2 infection had significantly lower levels of NT-proBNP compared to those with evidence of infection (via a positive Severe Acute Respiratory Syndrome Coronavirus 2 polymerase chain reaction or immunoglobulin G serology results), with respective NT-proBNP concentration medians of eleven pg/ml and 1,140 pg/ml.¹¹¹

Further, elevated circulating concentrations of NT-proBNP were also associated with a spectrum of cardiac manifestations in the paediatric COVID-19 and Multisystem Inflammatory Syndrome in Children patients. Children with elevated cardiac biomarkers (troponin, NT-proBNP, and/or Creatine Kinase-MB) had higher chances of being diagnosed with myocarditis, coronary artery aneurysm, and other cardiac injuries.^{81,111} In fact, most studies in Table 3 suggest probing for cardiac injury upon testing high levels of NT-proBNP in a paediatric Multisystem Inflammatory Syndrome in Children or COVID-19 patient. Interestingly, the study by Abrams *et al.*⁷⁸ studied the association between clinical cardiac manifestations and different markers tested (fibrinogen, D-dimer, troponin, brain natriuretic peptide, NT-proBNP, C-reactive protein, and others). Odds ratio analyses showed that elevated concentrations of brain natriuretic peptide and NT-proBNP were most closely correlated with decreased cardiac function and myocarditis. Moreover, NT-proBNP and interleukin-6 were the only two markers correlated with coronary artery abnormalities, and not troponin or brain natriuretic peptide.⁷⁸ Although NT-proBNP and brain natriuretic peptide are both robust monitors of cardiac function, NT-proBNP seems to be more sensitive in detecting heart failure. Indeed, in a 2022 French study on paediatric patients with positive Severe Acute Respiratory Syndrome Coronavirus 2 tests, Raynor *et al.*⁸³ suggest that due to kinetic differences between the two molecules, NT-proBNP is to be favoured over brain natriuretic peptide in detecting heart failure, at least in Multisystem Inflammatory Syndrome in Children patients.

In most studies presented in Table 2, patients were retrospectively grouped on an outcome-related basis, generally between mild and severe cases, and ICU admission instances were considered moderate-to-severe. The parameter of interest, NT-proBNP, marked some interesting findings, where in almost all of the studies, its levels were consistently higher in accordance with severity. This means that for the most part, the more severe the health status of a cohort, be it a Multisystem Inflammatory Syndrome in Children, Kawasaki Disease, or any other cohort, the higher the NT-proBNP levels. Most studies did not report the actual change of NT-proBNP levels in patients over the course of the disease, but only retrospectively noted its value upon admission and compared it to the severity of the illness. However, according to the main findings, we can only conjecture that clinically, a sudden increase in NT-proBNP levels has to be correlated to greater severity of the cardiac manifestation in question, as the data suggest.

Unlike the case of adults, there is limited information pertaining to paediatric NT-proBNP COVID-19 cohorts, and therefore more studies need to be published. Also, additional biomarkers like troponin should be investigated, and more studies on paediatric COVID-19 and/or Multisystem Inflammatory Syndrome in Children populations should be carried out.

Conclusion

The COVID-19 pandemic incurred heavy burdens on the healthcare sector, and cardiovascular manifestations rapidly

Table 3. Study characteristics and major NT-proBNP findings in paediatric patients

Reference	Authors	Year published	Study Type	Country	Number of Cases	Method of patient grouping	Study Findings	Cardiac parameters assessed
123	Rekhtman et al.	2021	Descriptive cohort	USA	31	MIS-C versus non-MIS-C COVID-19 patients	MIS-C group showed significantly greater levels of NT-proBNP compared to non-MIS-C COVID-19 group	NT-proBNP, Troponin
107	Corwin et al.	2020	Retrospective	USA	32	Clinical outcome: mild, moderate (Kawasaki Disease), and critical	NT-proBNP levels increase with severity of COVID-19 clinical outcome	NT-proBNP, Troponin
111	Whittaker et al.	2020	Case series	England	58	Same patients stratified in multiple groups: Shock (\pm); CAA (\pm); Kawasaki Disease (\pm); PIMS-TS (\pm)	Shock and CAA group showed extremes of NT-proBNP levels; Above normal levels for PIMS group; Less marked elevation for Kawasaki Disease group	NT-proBNP, Troponin
108	Lee et al.	2020	Retrospective	USA	28	ICU admission (admitted or not admitted)	Patients requiring critical care had significantly more elevated levels of NT-proBNP compared to non-ICU patients. High BNP concentrations were correlated to lower EF.	NT-proBNP, Troponin
124	Prata-Barbosa et al.	2020	Prospective	Brazil	72	MIS-C versus non-MIS-C patients	All patients tested for NT-proBNP (7, MIS-C) showed elevated concentrations: Median – 5,829 pg/ml	Troponin; CK; CK-MB;
109	Jain et al.	2020	Observational study (unspecified)	India	23	PIMS-TS association with Shock (With Shock versus Without Shock)	The levels of NT-proBNP in the PIMS-TS shock group were significantly greater. They also showed increased needs of inotropic treatment.	Troponin, NT-proBNP
125	Diorio et al.	2020	Retrospective	USA	50	COVID-19 outcomes: Minimal, Severe COVID-19 and MIS-C groups	The MIS-C group showed significantly greater levels of NT-proBNP when compared to the Severe COVID-19 group	Troponin, NT-proBNP
126	Ozsurekci et al.	2021	Retrospective	Turkey	52	COVID-19 outcomes: Severe/critical COVID-19 and MIS-C groups	The MIS-C group showed significantly greater levels of NT-proBNP when compared to the severe/critical COVID-19 cohort	Troponin, NT-proBNP
78	Abrams et al.	2021	Retrospective	USA	1080	According to ICU admission: Admitted (same day of hospitalisation versus next day) and non-admitted	The whole cohort had a significantly high level of NT-proBNP: 2054 pg/ml (310 – 7,778) The ICU-Admitted group showed greater levels of NT-proBNP when compared to the non-admitted	Troponin, NT-proBNP, BNP
127	Abdel-Haq et al.	2020	Unspecified	USA	33	According to care requirements for MIS-C patients: Critical care versus Less intense care	The MIS-C cohort had significantly high level of NT-proBNP: 1,524.5 pg/ml (555 – 2,301) The Critical care group had significantly higher levels of NT-proBNP	Troponin, NT-proBNP
128	Girona-Alarcon et al.	2021	Prospective	Spain	4	COVID-19 patients formed one group: Admitted to ICU	The group had a high level of NT-proBNP: 4,057 pg/ml (2,629 – 18,211)	Troponin, NT-proBNP
83	Raynor et al.	2022	Retrospective	France	14	Cardiogenic shock (shock versus non-shock groups)	NT-proBNP and BNP levels were both significantly more elevated in the shock group	NT-proBNP, Galectin-3, BNP
129	G FC;ll FC; et al.	2021	Retrospective	Turkey	320	According to COVID-19 outcome: MIS-C versus non-MIS-C	The MIS-C group showed significantly greater levels of NT-proBNP compared to the non-MIS-C COVID-19 cohort	Troponin, NT-proBNP, CK-MB, CK
81	Pouletty et al.	2020	Retrospective	France	16	Severity of Kawasaki Disease associated with SARS-CoV-2 infection (severe versus non-severe)	All patients tested for NT-proBNP (n = 11) showed elevated concentrations with a median of 4319 pg/ml Notably, the Kawasaki Disease-COVID-19 severe group had lower BNP levels when compared to the non-severe group	Troponin, NT-proBNP

followed the pulmonary ones. The outreaching effects of these manifestations targeted both the adult and the paediatric populations, as the literature has shown. Clinical biomarkers as well as other diagnostic tools such as echocardiograms were at the disposition of the healthcare professionals to monitor the cardiac symptoms. NT-proBNP has demonstrated a clear correlation with a spectrum of cardiac implications, and it is generally considered superior to brain natriuretic peptide as a predictor of heart failure. The debate on whether NT-proBNP should replace echocardiography as a diagnostic tool for cardiac dysfunction post-COVID-19 is still ongoing, but the majority of studies have proven the evident association between the levels of this biomarker and heart problems without discriminating between age groups. We contend that more paediatric studies on existing data must be carried out, particularly those involving large cohorts of patients, in order to provide novel perspectives on whether NT-proBNP should be adopted as a main indicator for heart failure and other cardiovascular outcomes.

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