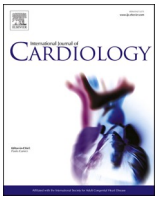
International Journal of Cardiology 421 (2025) 132723

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard



Clinical impact of circulating biomarkers in prediction of adverse cardiac events in patients with congenital heart disease. A systematic review

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ARTICLE INFO

Keywords:
Biomarkers
Prognosis
Congenital heart disease
Hs-TnT
CRP
ST-2
GDF-15
RDW
Albumin
Creatinine
Gal-3
Norepinephrine
BNP
NT-proBNP
MELD-XI

ABSTRACT

Introduction: Patients with congenital heart disease (ConHD) are at increased risk for adverse cardiac events. Predicting long-term outcomes and guidance of patient management might benefit from a range of (new) biomarkers. This is a rapidly evolving field with potentially large consequences for clinical decision making. With a systematic review of available biomarkers in ConHD we identified the clinical role of these markers, knowledge gaps and future research directions.

Methods: We systematically reviewed the literature on associations between blood biomarkers and outcome measures (mortality or composite adverse outcomes in patients with ConHD.

Results: The inclusion criteria were met by 102 articles. Biomarkers assessed in more than 3 studies are discussed in the main text, those studied in 3 or less studies are summarized in the supplement. Thus, we discuss 15 biomarkers from 92 studies. These biomarkers were studied in 32,399 / 10,735 patients for the association with mortality and composite adverse outcomes, respectively. Biomarkers that were studied most and had statistically significant associations with mortality or composite adverse outcomes were (NT-pro)BNP, MELD-XI score, Hs-CRP, creatinine, albumin and sodium. Most of these biomarkers are involved in intracardiac processes associated with inflammation or are markers of renal function.

Conclusion: For (NT-pro)BNP, clinical value for prediction of mortality and composite adverse outcomes in adult and paediatric ConHD has been shown. For MELD-XI, hs-CRP, albumin, creatinine, sodium, RDW, and GDF-15, correlations with mortality and composite adverse outcomes have been demonstrated in patient groups with mixed types of ConHD, but clinical utility needs additional exploration.

1. Introduction

Congenital heart disease (ConHD) is the most common birth defect, affecting around 1 % of newborns [1]. In recent decades the survival of patients with ConHD has increased due to improvements in antenatal screening, diagnostics, catheter interventions, surgical techniques, and supportive care. For common types of ConHD over 60 % of patients have residual lesions after initial (surgical) correction [2–5]. The combination

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https://doi.org/10.1016/j.ijcard.2024.132723
Received 20 August 2024; Received in revised form 29 October 2024; Accepted 8 November 2024
Available online 10 November 2024

of residual abnormalities and increased prevalence of ConHD results in a growing population at risk for long-term adverse events [6,7]. As many as 1 in 13 patients with ConHD will develop HF during their lifetime, and the risk of death after the age of 18 years is 3.2 times higher among ACHD patients compared to controls [8,9]. A major challenge in the follow-up of paediatric and adult patients with ConHD is to stratify the risk of who will develop complications [10]. Furthermore, there is a need to find new targets for screening, monitoring, (guidance of) drug therapy and endpoints for (drug) trials in paediatric patients [11]. This is a rapidly evolving field in which several pathways and related blood biomarkers of neurohormonal activation, myocardial injury and stress, inflammation, fibrosis, remodeling, vascularization and non-cardiac organ dysfunction have been discovered in ConHD [12–16]. Of these markers, B-type natriuretic peptide (BNP) and N-terminal segment of pro-BNP (NT-proBNP) have been included [17] in current guidelines for patients with ConHD, contributing to assessment of prognosis and indications for interventions [11,18]. Recently several new markers have been reported, providing new and additional information on pathways related to outcome measures in ConHD [19]. In this paper, we examined the (potential) clinical role of these markers by systematic review, aiming to identify their current clinical role, knowledge gaps and potential future research directions.

2. Methods

2.1. Search strategy

A systematic search of the Embase, Medline, Web of Science Core Collection and Cochrane Central Register of Controlled Trials databases was performed on 14th of June 2023 to identify studies on the prognostic value of blood biomarkers in patients with ConHD. The exact search strategy used is given in *Supplementary Text 1*.

2.2. Eligibility of studies

All articles were screened by title and abstract and assessed independently by two reviewers (QD and HA). Discrepancies were resolved by discussion with a third reviewer (WG). Subsequently full-texts of included articles were read. Studies were included if they were written in English, studied patients with ConHD across the paediatric and adult age range, were cohort studies or clinical trials with a minimum follow-up of six months, evaluating the prognostic value of blood biomarkers on the prognostic endpoints mortality or composite adverse outcomes. We included studies if composite adverse outcomes was defined as the occurrence of all-cause mortality, heart failure, (re)hospitalization for cardiac reasons, arrhythmia, heart transplantation, pulmonary arterial hypertension (PAH), liver or kidney failure, impaired exercise tolerance (decreased peak oxygen uptake (VO2) or cardiac re-interventions, or a combination of the above.

2.3. Inclusion

We list all studies that fulfilled the inclusion criteria and their data (*supplementary Table 1 & 18–37*) but, for practical reasons, we opted to discuss only those biomarkers that were studied in at least 4 different studies, irrespective of the type of patients included in the full text of this paper.

2.4. Data extraction

The following information was extracted from the included articles: type of ConHD, number of participants, male/female distribution, mean or median age, the biomarkers studied, prognostic endpoints, follow-up duration, and measures of the association between the biomarkers and the study endpoints.

2.5. Statistical analysis

Studies were aggregated that a) included a mixture of ConHD conditions, b) focussed on a specific ConHD condition and c) evaluated patients with ConHD complicated by PAH. Studies were classified as 'paediatric' if the mean or median age of study subjects was below 18 years, and as 'adult' otherwise. The Quality in Prognostic Studies tool was utilized to assess risks of bias of individual studies, screening was done by one of 3 authors (WG, QD, HA) [20].

In case 95 % confidence intervals (CIs) of effect sizes were not reported in the included studies, these were calculated using other data in the manuscript or extracted from graphs if possible from the available data. Results were considered significant if $p < 0.05$.

3. Results

3.1. Study characteristics

A total of 102 articles fulfilled the inclusion criteria (Fig. 1). A complete overview of the number of studies per biomarker is provided in Fig. 2. Two thirds of studies included have been published after 2017. Applying the criterion for discussion of at least 4 available studies per biomarker, we will report on 92 studies (44 in mixed types of ConHD, 9 on ConHD with PAH, 17 in specific ConHD types, of which 10 in Fontan patients). An overview of all included studies with their main characteristics is shown in *Supplementary Table 1 & 2* [12,21–115].

Detailed information on patient characteristics, type of biomarker, outcome measures and percentage of outcome reached for all the 92 included studies can be found in *Supplementary Table 3–37*. Results of the quality assessment can be found in *Supplementary Table 38–39*. We utilized the Quality in Prognostic Studies (QiPS) score to appreciate quality of the included studies [20]. On average studies done in adults were of higher quality (2.61 ± 0.44) compared to paediatric studies (2.35 ± 0.48) (Table 1). In general most studies scored well on most points except in correction for confounding.

From 92 articles, a total of 32,399 patients were included in mortality analysis and 10,735 patients were included for analysis of composite adverse outcomes. The number of patients per biomarker studied for the association with mortality and composite adverse outcomes is depicted in Fig. 3. On average 331 patients were included per study. The average number of patients per type of cohort was: 530 for mixed ConHD diagnostic types, 162 for studies on single ConHD types (165 for Fontan patients) and 102 for studies analyzing ConHD with PAH. Paediatric studies included a mean number 151 participants, in adults this was 371.

3.2. Biomarkers and mortality

The median follow-up between time of biomarker assessment and reaching an endpoint (mortality or composite adverse outcomes) was 4.25 years (IQR range 2.43–6.13 years). As shown in Fig. 3A, MELD-XI score, (NT-pro) BNP creatinine, albumin and sodium were all studied in large numbers of patients (> 3000 patients / marker included) and showed mostly significant associations with mortality. Hs-CRP, norepinephrine and RDW were studied in relatively large cohorts. These biomarkers also had statistically significant associations with mortality in almost all studies. Platelet count, and Gal-3 were studied in smaller cohorts, mostly with a significant association with mortality. Uric acid was studied in a relatively large cohorts (± 1000 participants in total) but showed no association with mortality in over half of the patients.

In mixed cohorts (Fig. 4A), results were very similar to the overall group. Fig. 5A shows that the outcomes in disease-specific cohorts differed from those of the overall population. In disease specific cohorts norepinephrine was frequently studied and uric acid was the marked that most often showed significant results. Biomarkers ST2, Hs-CRP, GDF-15, and Gal-3 were studied less frequently and their correlations

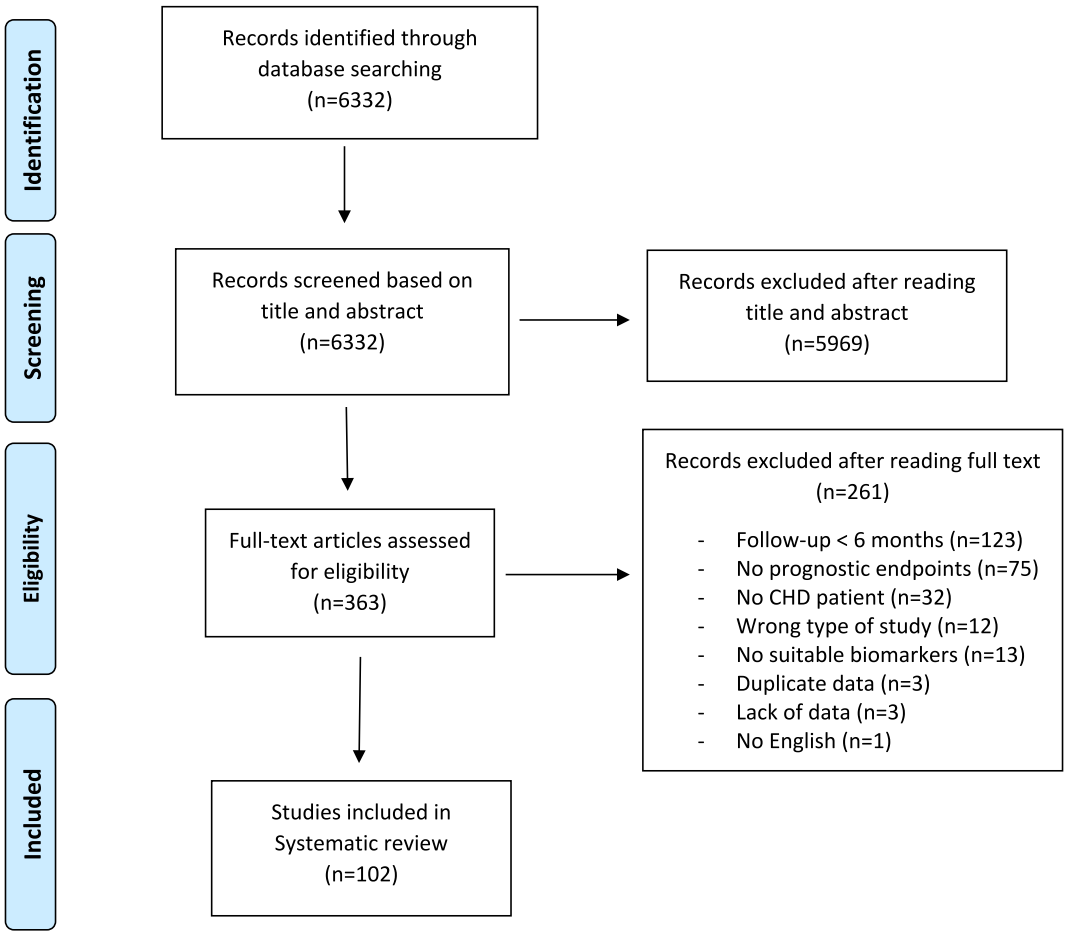

Fig. 1. Flowchart.

were not found to be significant in contrast to in overall populations.

In patients with PAH in ConHD, the biomarkers (NT-pro) BNP, hs-CRP, creatinine, hs-TnT, RDW, uric acid and Gal-3 were shown to have significant associations with mortality (Fig. 6A).

Fig. 7A and 8A show an overview of studies of biomarkers in different age groups. 29,676 adult patients were studied. As this is the most studied group these results are very comparable to the overall cohort. 2723 children were studied. NT-proBNP, norepinephrine and uric acid were studied in large patient numbers with significant association with mortality. For hemoglobin, Hs-CRP, GDF-15 and Hs-Tnt no association with mortality was noted. ST2, Gal-3 and platelet count showed positive association with mortality, in relatively small patient numbers.

3.3. Biomarkers and composite adverse outcomes

An overview of the number of patients studied with composite adverse outcomes as outcome marker is given in Fig. 3B. (NT-pro) BNP was by far the most studied biomarker with a significant association in most studies. In mixed cohorts (Fig. 4B) and disease specific cohorts (Fig. 5B) (NT-pro) BNP was most frequently studied, with relatively more non-significant studies in disease specific cohorts compared to mixed cohorts and patients with CHD-PAH (Fig. 6B). Hs-TnT, albumine and Hs-CRP were also studied frequently. For these markers a significant association with composite adverse outcomes was found in around 2/3 of patients. Albumine and Hs-CRP were not studied in disease specific cohorts (Fig. 5B). In mixed cohorts albumin and creatinine were extensively studied, however in around half of the patients no significant association was found. For Patients with PAH in ConHD (Fig. 6B creatinine, Hs-TNT and (NT-pro) BNP showed a significant association with composite adverse outcomes in all.

4. Discussion

The study of biomarkers in ConHD is a rapidly evolving field with potentially large consequences for clinical decision making. This systematic review has provided an overview of available biomarkers is ConHD. The strongest evidence is for the predictive value of (NT-pro) BNP in both predicting mortality and composite adverse outcomes in adult and paediatric ConHD. For other markers reviewed, correlations with mortality and composite adverse outcomes have been demonstrated in patient groups with mixed types of ConHD. The evidence for these biomarkers to predict adverse outcomes varies by biomarker and by type of diagnosis.

A summary of the mechanisms of action of the biomarkers studied in this review is given in Table 2. In general, these mechanisms have been described extensively in acquired heart disease [116–141].

Blood biomarkers may play an important role in risk stratification for mortality and composite adverse outcomes and may improve monitoring, treatment guidance and the understanding of pathophysiology. The associations with mortality and composite adverse outcomes in ConHD will be discussed for the different biomarkers emerging from the systematic review in the following. Knowledge gaps exist for other roles of these biomarkers, as will be discussed subsequently.

4.1. Cardiac associated biomarkers

In ConHD (NT-pro) BNP has been studied extensively. This is the

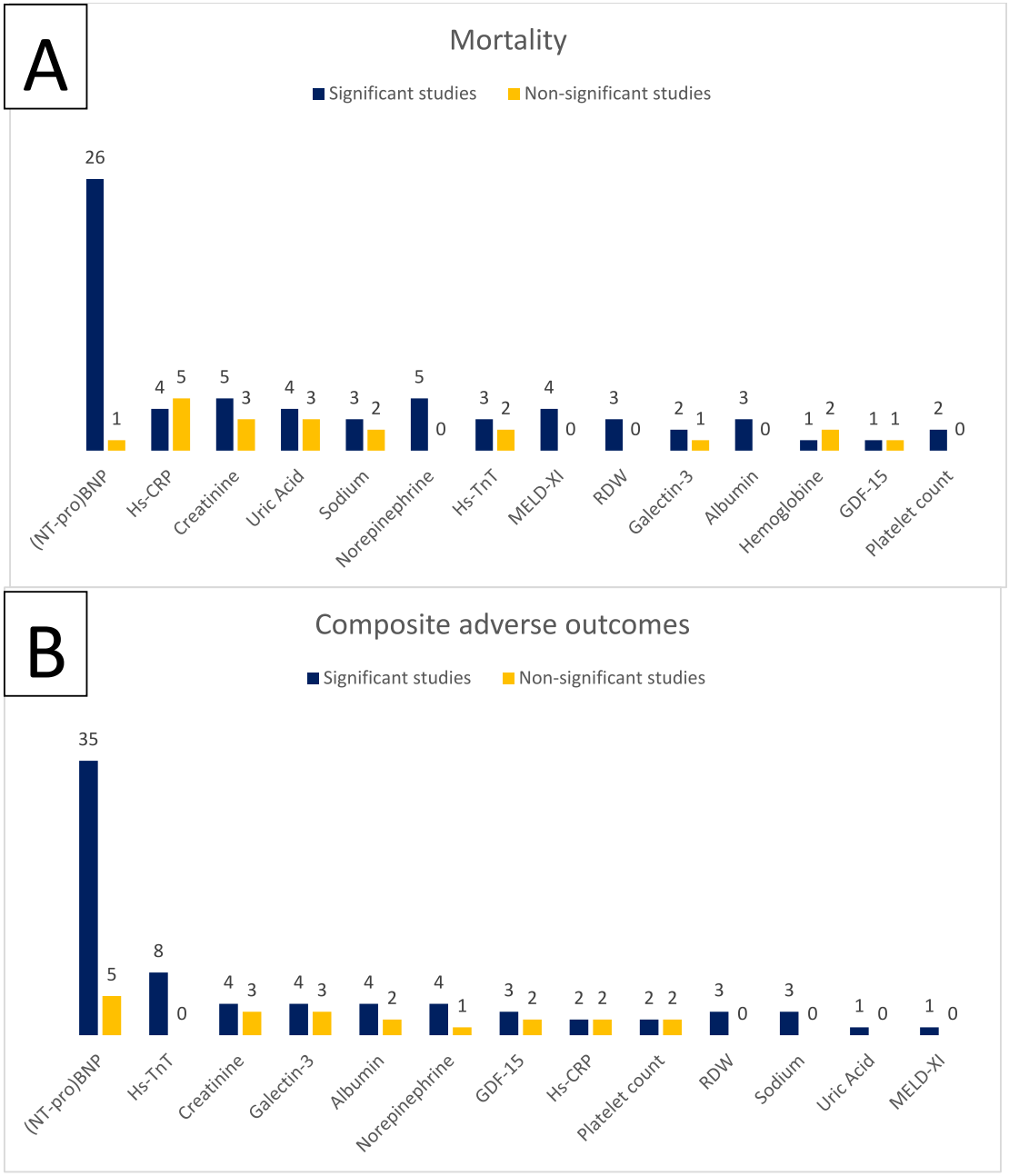

Fig. 2. Number and significance level for association with outcome measures mortality (panel A) and composite adverse outcomes (panel B) of studies per biomarker in ConHD**.**

Abbreviations: (**NT-pro)BNP**: N-terminal pro b-type natriuretic peptide; **Hs-TnT**: High-sensitivity troponin T; **Hs CRP**: High-sensitivity C-reactive protein; **RDW**: Red cell distribution width; **ST2**: suppression of tumourigenicity 2; **MELD score**: Model for End-Stage Liver Disease score**; GDF-15**: Growth differentiation factor 15; **ConHD**: congenital heart disease; **PAH**: pulmonary arterial hypertension. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

only biomarker currently included in adult ConHD guidelines [40,44,47,142–144]. It was shown to have strong associations with mortality and composite adverse outcomes in all different groups, both in adult and paediatric cohorts, making it the best available marker for adverse events in ConHD at present.

For hs-TnT there was a strong association between increased levels and both composite adverse outcomes and mortality in PAH-ConHD patients [65,77] and in patients with ccTGA, with univentricular hearts, and in cohorts with mixed types of ConHD disease. The added value of Hs-TnT in predicting composite adverse outcomes in patients with ConHD and PAH is less clear [21,31,39,65,77,87]. In paediatric cohorts the predictive value of Hs-TnT was low whereas in adults there was predictive value. Hs-TnT is mainly released as a response to cell damage often as a result of inadequate oxygen supply to the myocardium [145]. We speculate that children might be better able to maintain adequate oxygen supply to the tissues where adults have developed more myocardial damage over time, e.g. resulting in more myocardial fibrosis, in combination with deterioration of coronary artery function [146–148].

Gal-3 was associated with mortality in relatively small cohorts of mixed ConHD. In relatively large mixed ConHD cohorts, Gal-3 was associated with composite adverse outcomes. No significant association with mortality was observed in disease-specific cohorts. See paragraph on limitations of the available studies.

Table 1
overview of the association of described biomarkers with different disease conditions.

	Myocardial stretch	Myocardial injury	Myocardial fibrosis	Chronic inflammation	Renal dysfunction	Hepatic dysfunction	Nutritional deficiencies	Endothelial dysfunction	Oxygen free radicals	Adverse remodeling	Coagulation
(NT-pro)BNP	+										
Hs-TnT		+									
Galactin 3			+	+							
Hs CRP				+							
RDW				+	+	+	+	+			
ST2	+			+						+	
Uric acid				+	+			+	+		
MELD score					+	+					
Albumin				+	+	+		+			
Norepinephrine										+	
Platelet count				+		+					+
GDF-15		+		+							

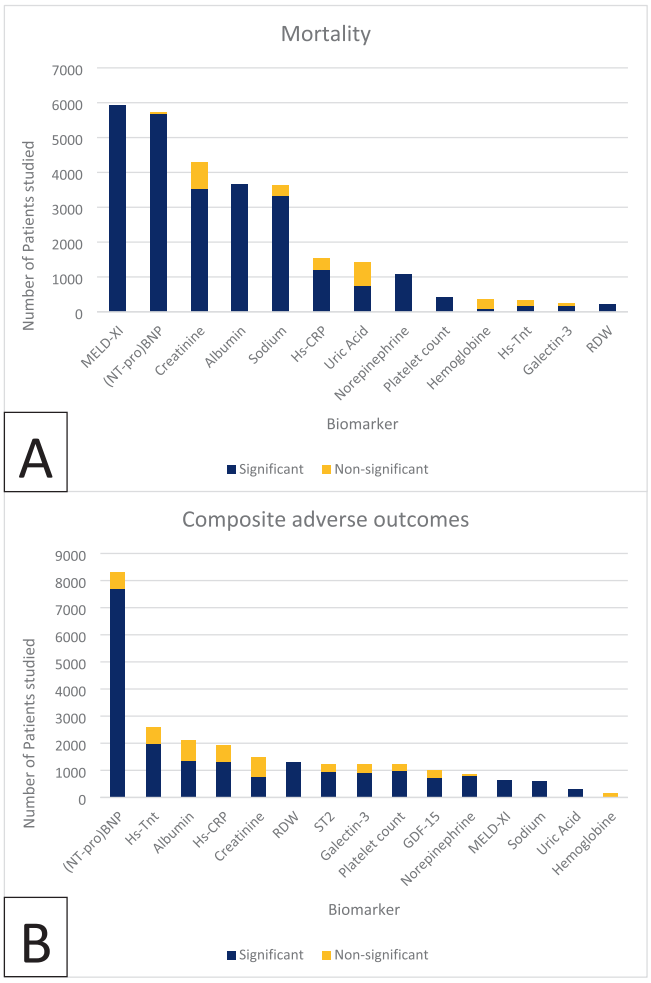

Fig. 3. Number of patients and significance level per biomarker for association with outcome measures mortality (panel A) and composite adverse outcomes (panel B), overall.

4.2. Markers of inflammation

For Hs-CRP associations with mortality were significant in a majority of patients for both mixed and PAH-ConHD cohorts. However, in the only disease specific cohort, patients with tetralogy of Fallot, no association with mortality was found, probably related to the small number of patients reaching the endpoint.

Significantly higher risk for mortality with increased RDW was found in mixed types ConHD and in patients with ConHD related PAH [45,109]. RDW was not studied in disease specific cohorts.

For ST2 60 % of the studies, including a large study in a mixed ConHD cohort, found an association with composite adverse outcomes. Two studies in disease specific cohorts did not find this association.

For hyperuricemia, 2 out of the 4 studies showed a significant association between mortality and higher uric acid levels for patients with a Fontan circulation and in ConHD patients with PAH [98,99]. The only mixed-ConHD cohort in which uric acid was studied did not show a significant association [81].

4.3. Renal function associated biomarkers

In general, creatinine showed strong associations with mortality in all types of cohorts. However, associations with composite adverse outcomes were less clear.

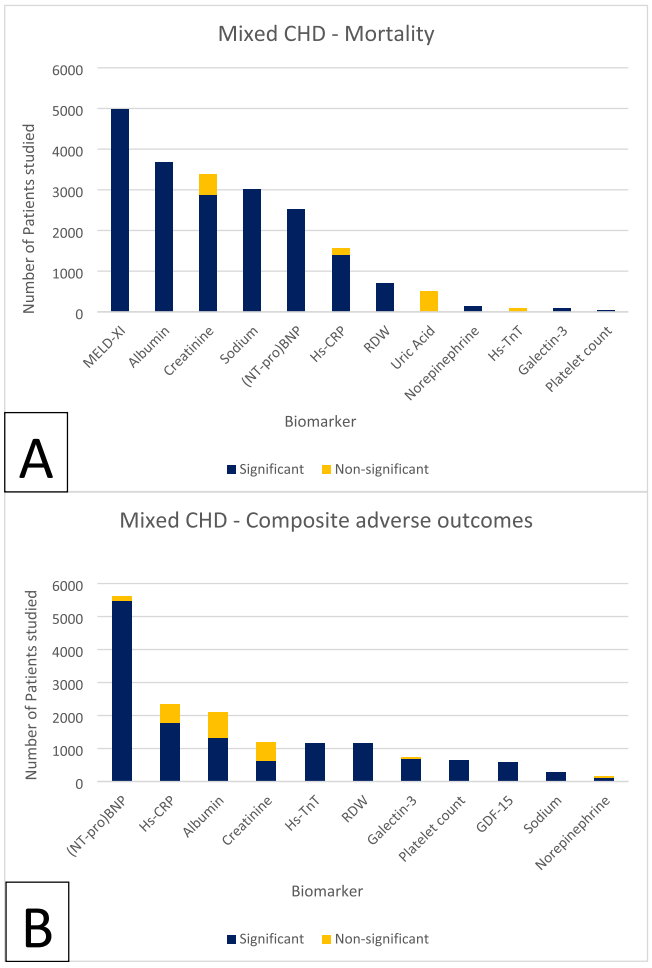

Fig. 4. Number of patients and significance level per biomarker for association with outcome measures mortality (panel A) and composite adverse outcomes (panel B) for the number of patients per biomarker, in studies of cohorts with mixed types of congenital heart disease.

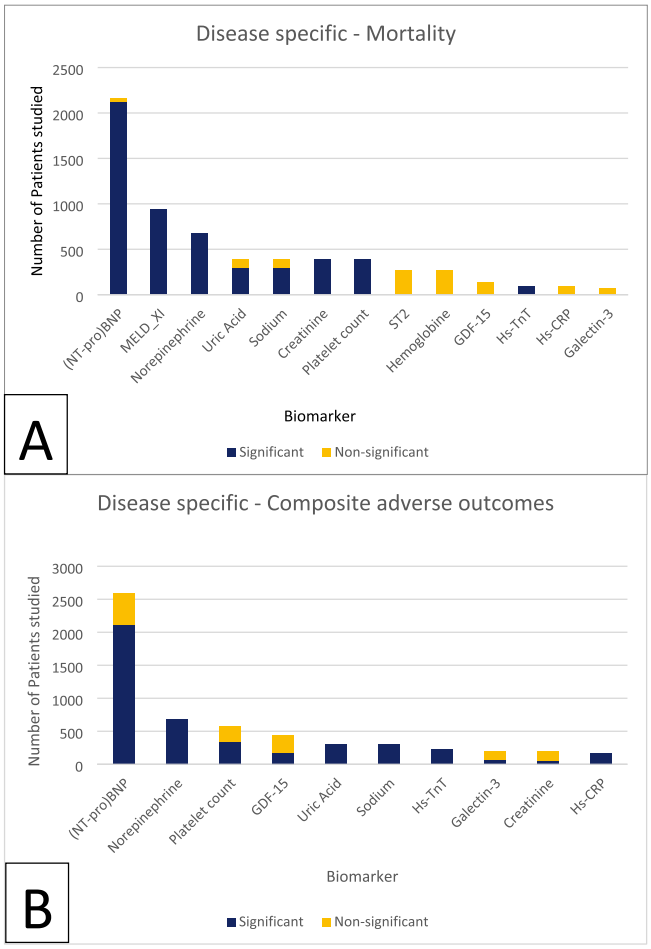

Fig. 5. Number of patients and significance level per biomarker for association with outcome measures mortality (panel A) and composite adverse outcomes (panel B) for the number of patients per biomarker, in studies of cohorts with specific ConHD.

4.4. Other biomarkers

Albumin has been associated with adverse events in ConHD, related to increased central venous pressure, a known complication of many different types of ConHD [149,150] [149,150]. Increased central venous pressure may lead to a shift in albumin from intracellular to the extracellular space [84]. Hypoalbuminemia is probably also influenced by chronic inflammation and endothelial dysfunction [151], which have also been related to complications of different types of ConHD [152]. However, significant associations between albumin levels and mortality and composite adverse outcomes were only found in mixed cohorts of ConHD, probably related to the wide range of central venous pressures and inflammation levels in specific groups [152].

Our review showed an association between norepinephrine and mortality and composite adverse outcomes in almost 1000 patients with Fontan circulation [55,85,98]. However, norepinephrine was not studied in other ConHD populations. Because of the unique physiology of the Fontan circulation, we cannot extrapolate these results beyond Fontan patients.

Platelet count is associated with all-cause mortality in the general population as well as in patients with cardiovascular disease [153,154]. This is thought to be caused by changes in coagulation and inflammation [102]. An increased risk of composite adverse outcomes was found in Fontan patients [50]. However, composite adverse outcomes in this study was mainly driven by liver cancer, a complication of Fontan associated liver disease [6]. Platelet count is decreased in patients with liver failure and portal hypertension [155]. Therefore, in Fontan patients, platelet count might reflect liver rather than cardiac.

The MELD-XI score is a combination of creatinine, bilirubin and INR, indicating hepatorenal function [3]. Whilst this biomarker score was studied in only 5 studies, the number of included patients was high (> 5000), mainly driven by large studies in mixed cohorts and in Ebstein's disease [113,156]. The predictive value of MELD-XI for mortality has also been shown in Fontan patients, known for liver problems [157]. Evidence for MELD-XI as risk predictor is lacking in patient groups without liver complications.

Considering its documented role in acquired heart disease GDF-15 is a promising biomarker with demonstrated association with all-cause mortality and composite adverse outcomes in mixed cohorts of ConHD patients [123–125]. However, in disease specific ConHD cohorts, mostly non-significant results have been shown. Therefore, it remains uncertain how useful GDF-15 is as a predictor for adverse events in ConHD.

4.5. Biomarkers studied in less than 4 studies

59 biomarkers were studied in less than 4 studies, 18 of these biomarkers were cardiac associated biomarkers, 9 were markers of inflammation, 8 were associated to renal function and 22 could be classified as other biomarkers (See Tables 19–37 in supplemental material). Often these biomarkers were closely related to biomarkers studied more frequently. For example bilirubin (studied 1 time) is part of

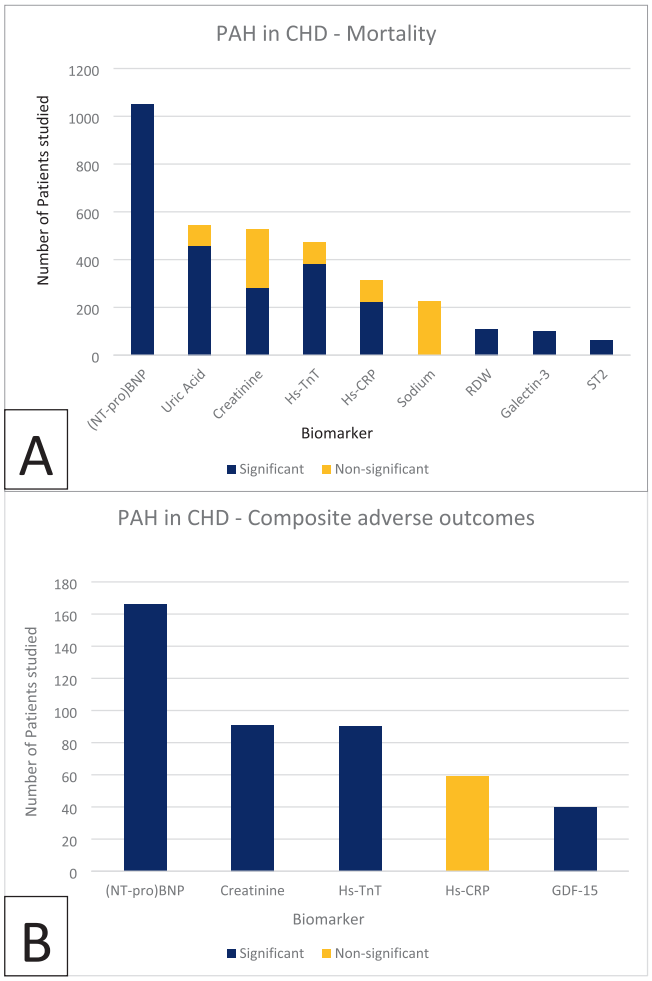

Fig. 6. Number of patients and significance level per biomarker for association with outcome measures mortality (panel A) and composite adverse outcomes (panel B) for the number of patients per biomarker, in studies of cohorts of ConHD with PAH.

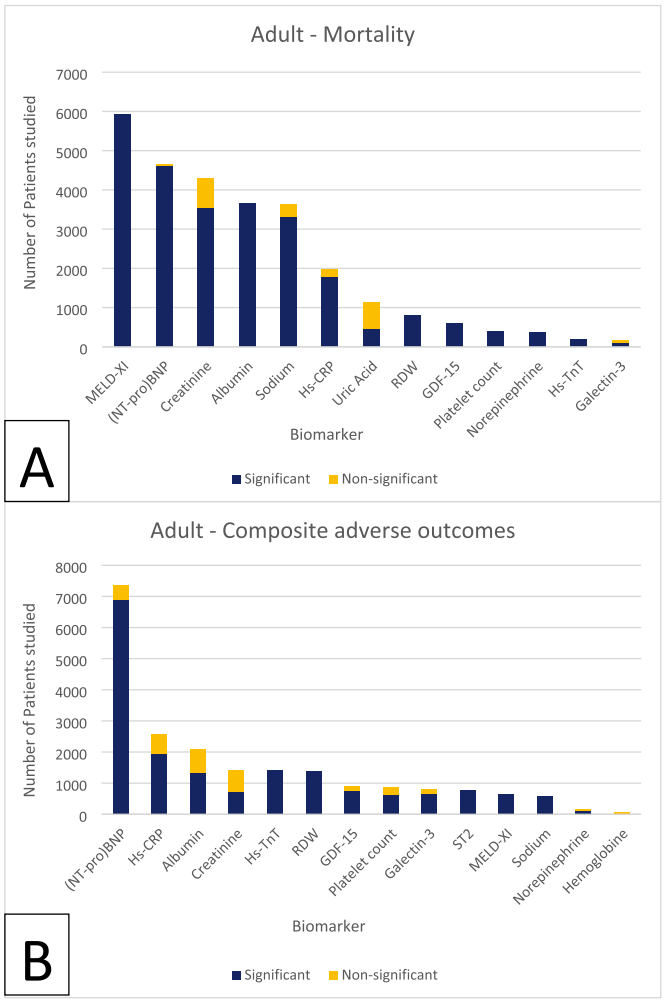

Fig. 7. Number of patients and significance level per biomarker for association with outcome measures mortality (panel A) and composite adverse outcomes (panel B) for the number of patients per biomarker, in studies of cohorts in adult ConHD patients.

the MELD-XI score and ANP (studied 3 times) is closely related to (NT-pro)BNP . The studies in this group of less frequently studied biomarkers in general were smaller (115 participants vs 330 participants for studies studying more frequently studied biomarkers). Often these less frequently studied biomarkers have only studied by one specific research group, which reduces generalizability and increases the risk for bias.

4.6. *Knowledge gaps and directions for future research*

Currently available studies in ConHD have not answered relevant questions like:

i) What type of use of additional biomarkers in addition to (NT-pro) BNP is predictive of outcomes (e.g. baseline values, serial measurements, combinations of different biomarkers, changes with therapy)?

It has been suggested that combining several markers increases the predictive value for heart failure risk in adult ConHD [158,159]. However, most reviewed studies focused on a single biomarker and its association with mortality and/or composite adverse outcomes. Some studies (*Supplementary Table 1 & 2*) have tested and shown the additional predictive value beyond (NT-pro)BNP [12]. In a study by Baggen et al. the authors combined three different biomarkers (NT-pro)BNP, Hs-TnT and GDF-15) and showed that patients who had no biomarkers elevated had an event free survival of 86 % over 4 years, whereas in patient where all 3 biomarkers were elevated only 27 % was without adverse events over 4 years. Often it has been difficult to show additive value of biomarkers over NT-proBNP [106]. Therefore we advise that all new biomarkers should at least be tested on their added value beyond NT-proBNP. Lastly we hypothesize that biomarkers based on different organ systems could provide added value when combined.

A versatile approach in managing ConHD in adults involves combining blood biomarkers with other clinical data to create a risk score, used for screening, monitoring, treatment guidance and risk prediction, as demonstrated in recent studies [160]. These aspects require further evaluation in adults and children with ConHD,s shown by the lack of confounding correction seen in the studies included in this review.

ii) what is the impact on clinical decision making of potential natural fluctuations in biomarker levels and of confounders in assessment (e.g. age, sex, obesity, renal function)?

In a recent review on the use of biomarkers in children with ConHD, McGinn et al. pointed towards the lack of age-related reference rates for many of the biomarkers discussed, except (NT-pro)BNP and troponin [161]. In acquired heart failure in adults, the importance of confounders of biomarker levels such as obesity has been stressed [162]. These

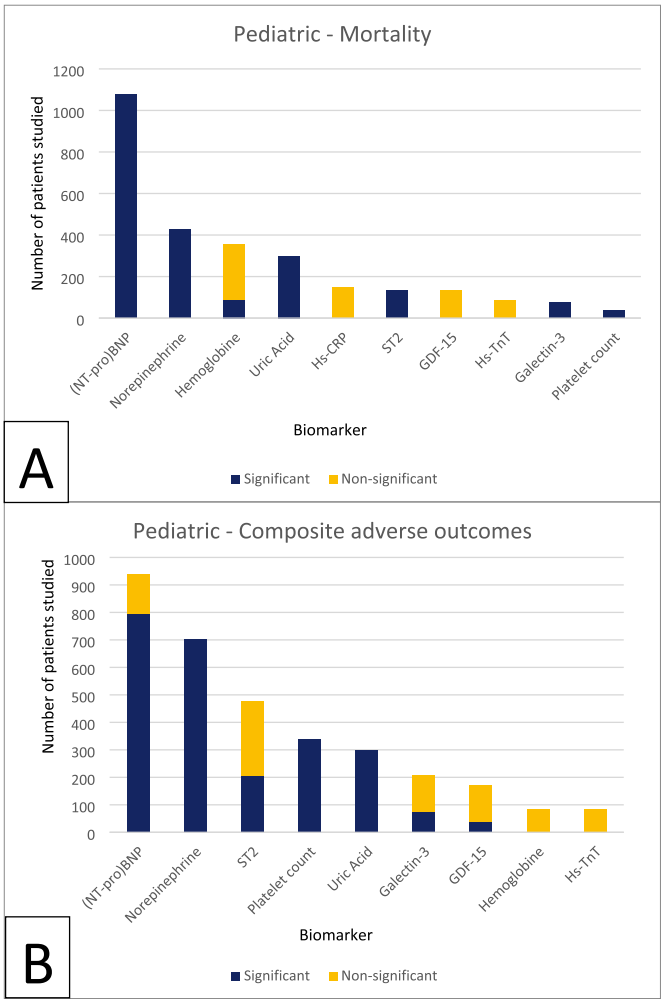

Fig. 8. Number of patients and significance level per biomarker for association with outcome measures mortality (panel A) and composite adverse outcomes (panel B) for the number of patients per biomarker, in studies of cohorts in paediatric ConHD patients.

factors have hardly been explored in patients with ConHD.

iii) does clinical decision making based on serum biomarkers improve outcomes for patients?

This important step has not been studied yet in ConHD and therefore it is unknown if implementation of these biomarkers leads to better identification of at-risk patients.

iv) which biomarkers may serve as endpoint or therapeutic targets in (drug) trials?

Biomarkers may have a role in developing optimal drug therapy with ConHD, e.g. by serving as surrogate endpoint [163]. Biomarkers, e.g. (NT-pro)BNP, have been established as adequate surrogate endpoints in adults with acquired with heart failure [164]. It is hard to reproduce similar studies in children with ConHD, mainly because hard endpoints are only obtained at long-term. In these cases biomarkers might be utilized as surrogate endpoints to bridge known effects in adults to children. In a few paediatrics drug trials, circulating biomarkers have been used as (surrogate) endpoints in cardiomyopathy [164]. In a randomized trial of ivabradine in children with heart failure from dilated cardiomyopathy (DCM) NT-proBNP was used a secondary outcome [165]. For the biomarkers in the population of ConHD, additional studies are required to determine their potential as bridging biomarker, since several of the required criteria cannot be derived from the reviewed studies [163]. NT-pro BNP in all groups, norepinephrine in Fontan patients, or Hs-TnT in patients with PAH in ConHD are promising in this respect, considering their strong patient-level association between the biomarker and FFS endpoints, particularly death and reinterventions [163].

v) what are the effects of interventions and changes in biomarkers on outcomes and what is the dynamic of these changes that are predictive of changed (improved) outcomes [166]?

This has not been studied yet.

vi) which biomarkers can be implemented in clinical guidelines?

Of the biomarkers discussed in this study, clinical value for prediction of mortality and composite adverse outcomes in adult and paediatric ConHD has been shown for (NT-pro)BNP, which has translated into various clinical guidelines. For MELD-XI, hs-CRP, albumin, creatinine, sodium, RDW, and GDF-15, correlations with mortality and adverse outcome have been demonstrated in patient groups with mixed types of ConHD, making them potential candidates to be included in guidelines for adults with ConHD, but not (yet) in specific lesions or in children. Apart from the limitations discussed in the items i – v, heterogeneity of the test populations and the lack of validation cohorts independently confirming the relationship between specific biomarkers and outcomes are issues to be addressed before biomarkers can be included in clinical guidelines.

4.7. Limitations

Based on the available literature meta-analysis was not possible. The high variability in the reporting of outcome measures and biomarker levels, such as the use of quartiles versus continuous risk either in a linear or logarithmic scale, hampered meta-analysis of biomarkers. In NT-pro(BNP) sufficient studies reported a continuous risk to execute a meta-analysis. However hazard ratio appeared strongly dependent on baseline level of (NT-pro) BNP. Arranging results according to baseline levels of NT-proBNP would result in small number of studies per meta-analysis or in high levels of heterogeneity in a single meta-analysis. We advocate future studies to report on hazard ratios (HR) for

Table 2
Aggregated averages for quality scores of QUIPS (full scores in supplementary tables 37–38).

	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting	Risk of bias
Paediatric studies							
Mean	2,53	2,65	2,76	2,65	2,00	2,65	2,35
SD	0,50	0,59	0,42	0,59	0,59	0,48	0,48
Adult Studies							
Mean	2,49	2,20	2,73	2,84	2,26	2,67	2,61
SD	0,57	0,48	0,44	0,37	0,69	0,62	0,44

biomarkers in a standardized way, preferably HR per increase of standard deviation on a logarithmic scale. Meta-analyses could also not be performed due to the heterogeneity in study populations, outcome definitions of the individual studies or lack of data.

Relatively few studies on blood biomarkers have been conducted in children. This hampers identification of early predictors of mortality and composite adverse outcomes in children with ConHD.

Most of the work we reviewed was based on single marker assessment. Potentially important markers may have been missed by this approach. Explorative tools, like e.g. targeted bioarray proteomics and metabolomics, may play an important role in further clarifying pathophysiology of heart failure in ConHD [67,167–172].

Most of the included studies in this systematic review are characterized by study populations heterogeneous for type of ConHD, age of the patients, follow-up duration and means of reporting of HR. Most of the studies involved relatively small study populations and may have been underpowered to establish significant associations bet.

een biomarker levels and the prognostic outcomes. Some studies included results on heart failure and mortality in the results for composite adverse outcomes.

5. Conclusion

Biomarkers in ConHD have been studied frequently and increasingly, mostly in mixed cohorts of adult patients with ConHD. For (NT-pro) BNP, clinical value for prediction of mortality and composite adverse outcomes in adult and paediatric ConHD has been shown, which has translated into various clinical guidelines. For MELD-XI, hs-CRP, albumin, creatinine, sodium, RDW, and GDF-15, correlations with mortality and composite adverse outcomes have been demonstrated in patient groups with mixed types of ConHD, not in specific ConHD types and paediatric cohorts.

Further studies are required to explore the role of additional blood biomarkers as a tool for screening, monitoring, treatment guidance and risk stratification in (paediatric) ConHD.

Disclaimer

The publication reflects the authors' views and neither IMI nor the European Union, EFPIA, or any Associated Partners of Conect4Children (C4C) are responsible for any use that may be made of the information contained therein.

CRediT authorship contribution statement

W.J. van Genuchten: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **H. Averesch:** Writing – review & editing, Data curation. **Q.M. van Dieren:** Writing – review & editing, Formal analysis, Data curation. **D. Bonnet:** Writing – review & editing, Conceptualization. **M. Odermarsky:** Writing – review & editing, Investigation. **M. Beghetti:** Writing – review & editing, Investigation. **J.W. Roos-Hesselink:** Writing – review & editing, Investigation. **Z. Reinhardt:** Writing – review & editing, Investigation. **C. Male:** Writing – review & editing, Investigation. **E. Naumburg:** Writing – review & editing, Investigation. **E. Boersma:** Writing – review & editing, Methodology. **D. De Wolf:** Writing – review & editing, Investigation, Conceptualization. **W.A. Helbing:** Writing – original draft, Resources, Formal analysis, Conceptualization.

Acknowledgement

The authors wish to thank M. Udo from the Erasmus MC Medical Library for developing and updating the search strategies.

Funding

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 777389. The Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.

WJ van Genuchten was supported by the Netherlands Cardiovascular Research initiative: an initiative with support of the Dutch Heart Foundation and Hartekind (grant to WA Helbing as part of a consortium; CVON219-002 OUTREACH).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2024.132723.

References

[1] Y. Liu, S. Chen, L. Zuhlke, G.C. Black, M.K. Choy, N. Li, B.D. Keavney, Global birth prevalence of congenital heart defects 1970-2017: updated systematic review and meta-analysis of 260 studies, Int. J. Epidemiol. 48 (2) (2019) 455–463.

[2] A.J. Marelli, A.S. Mackie, R. Ionescu-Ittu, E. Rahme, L. Pilote, Congenital heart disease in the general population: changing prevalence and age distribution, Circulation 115 (2) (2007) 163–172.

[3] K. Norozi, A. Wessel, V. Alpers, J.O. Arnhold, S. Geyer, M. Zoege, R. Buchhorn, Incidence and risk distribution of heart failure in adolescents and adults with congenital heart disease after cardiac surgery, Am. J. Cardiol. 97 (8) (2006) 1238–1243.

[4] S. Arnaert, P. De Meester, E. Troost, W. Droogne, L. Van Aelst, J. Van Cleemput, et al., Heart failure related to adult congenital heart disease: prevalence, outcome and risk factors, ESC Heart Fail 8 (4) (2021) 2940–2950.

[5] M. Nathan, J.C. Levine, M.I. Van Rompay, L.M. Lambert, F.L. Trachtenberg, S. D. Colan, et al., Impact of major residual lesions on outcomes after surgery for congenital heart disease, J. Am. Coll. Cardiol. 77 (19) (2021) 2382–2394.

[6] J.P.G. van der Ven, E. van den Bosch, A. Bogers, W.A. Helbing, State of the art of the Fontan strategy for treatment of univentricular heart disease, F1000 Res. (2018) 7.

[7] J.P.G. van der Ven, E. van den Bosch, A. Bogers, W.A. Helbing, Current outcomes and treatment of tetralogy of Fallot, F1000 Res. (2019) 8.

[8] N. Bergh, K. Skoglund, M. Fedchenko, E. Bollano, P. Eriksson, M. Dellborg, et al., Risk of heart failure in congenital heart disease: a nationwide register-based cohort study, Circulation 147 (12) (2023) 982–984.

[9] M.D. Dellborg, W.G.K. Giang, P.E. Eriksson, H.L. Liden, M.F. Fedchenko, A. A. Ahnfelt, et al., Long-term survival in adults with congenital heart disease: a nationwide, register-based cohort study, Eur. Heart J. 43 (Supplement_2) (2022).

[10] K.K. Stout, C.J. Daniels, J.A. Aboulhosn, B. Bozkurt, C.S. Broberg, J.M. Colman, et al., 2018 AHA/ACC Guideline for the management of adults with congenital heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, J. Am. Coll. Cardiol. 73 (12) (2019) 1494–1563.

[11] H. Baumgartner, J. De Backer, S.V. Babu-Narayan, W. Budts, M. Chessa, G. P. Diller, et al., 2020 ESC Guidelines for the management of adult congenital heart disease, Eur. Heart J. 42 (6) (2021) 563–645.

[12] V.J. Baggen, A.E. van den Bosch, J.A. Eindhoven, A.W. Schut, J.A. Cuypers, M. Witsenburg, et al., Prognostic value of N-terminal pro-B-type natriuretic peptide, troponin-T, and growth-differentiation factor 15 in adult congenital heart disease, Circulation 135 (3) (2017) 264–279.

[13] L.W. Geenen, V.J.M. Baggen, A.E. van den Bosch, J.A. Eindhoven, J. Cuypers, M. Witsenburg, et al., Prognostic value of soluble ST2 in adults with congenital heart disease, Heart 105 (13) (2019) 999–1006.

[14] P. Rodriguez, Y. Sassi, L. Troncone, L. Benard, K. Ishikawa, R.E. Gordon, et al., Deletion of delta-like 1 homologue accelerates fibroblast-myofibroblast differentiation and induces myocardial fibrosis, Eur. Heart J. 40 (12) (2019) 967–978.

[15] B.A. Fernandes, K.O. Maher, S.R. Deshpande, Cardiac biomarkers in pediatric heart disease: a state of art review, World J. Cardiol. 8 (12) (2016) 719–727.

[16] M. Abdel Raheem, W.F. Sedik, Prognostic value of soluble ST2 (SST2) serum levels in infants and children with heart failure complicating congenital heart disease, Int. J. Pediatr. 7 (5) (2019) 9471–9480.

[17] J.A. Eindhoven, A.E. van den Bosch, P.R. Jansen, E. Boersma, J.W. Roos-Hesselink, The usefulness of brain natriuretic peptide in complex congenital heart disease: a systematic review, J. Am. Coll. Cardiol. 60 (21) (2012) 2140–2149.

[18] N. Galie, M. Humbert, J.L. Vachiery, S. Gibbs, I. Lang, A. Torbicki, et al., 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT), Eur. Heart J. 37 (1) (2016) 67–119.

[19] N.E. Ibrahim, J.L. Januzzi Jr., Established and emerging roles of biomarkers in heart failure, Circ. Res. 123 (5) (2018) 614–629.
[20] J.A. Hayden, D.A. van der Windt, J.L. Cartwright, P. Cote, C. Bombardier, Assessing bias in studies of prognostic factors, Ann. Intern. Med. 158 (4) (2013) 280–286.
[21] M. Abu-Halima, E. Meese, M.A. Saleh, A. Keller, H. Abdul-Khaliq, T. Raedle-Hurst, Micro-RNA 150-5p predicts overt heart failure in patients with univentricular hearts, PLoS One 14 (10) (2019) e0223606.
[22] A.M. Atz, V. Zak, L. Mahony, K. Uzark, N. D'Agincourt, D.J. Goldberg, et al., Longitudinal outcomes of patients with single ventricle after the Fontan procedure, J. Am. Coll. Cardiol. 69 (22) (2017) 2735–2744.
[23] I.M. Blok, A.C. van Riel, M.J. Schuuring, R.H. de Bruin-Bon, A.P. van Dijk, E. S. Hoendermis, et al., The role of cystatin C as a biomarker for prognosis in pulmonary arterial hypertension due to congenital heart disease, Int. J. Cardiol. 209 (Journal Article) (2016) 242–247.
[24] L.J. Burchill, A.N. Redington, C.K. Silversides, H.J. Ross, L. Jimenez-Juan, S. Mital, et al., Renin-angiotensin-aldosterone system genotype and serum BNP in a contemporary cohort of adults late after Fontan palliation, Int. J. Cardiol. 197 (2015) 209–215.
[25] S.N. Chiu, K.P. Weng, M.C. Lin, J.N. Wang, B.T. Hwang, Z.K. Dai, et al., Congenital heart disease with pulmonary artery hypertension in an Asian cohort-initial report from TACHYON (TAiwan congenital heart disease associated with pulmonarY arterial hypertension) registry, Int. J. Cardiol. 317 (2020) 49–55.
[26] G.P. Diller, R. Alonso-Gonzalez, A. Kempny, K. Dimopoulos, R. Inuzuka, G. Giannakoulas, et al., B-type natriuretic peptide concentrations in contemporary Eisenmenger syndrome patients: predictive value and response to disease targeting therapy, Heart 98 (9) (2012) 736–742.
[27] K. Dimopoulos, G.P. Diller, E. Koltsida, A. Pijuan-Domenech, S.A. Papadopoulou, S.V. Babu-Narayan, et al., Prevalence, predictors, and prognostic value of renal dysfunction in adults with congenital heart disease, Circulation 117 (18) (2008) 2320–2328.
[28] J. Fan, Y. Qiu, Z. Zheng, L. Yu, S. Shi, X. Wu, NOD-like receptor protein 3 and high mobility group box-1 are associated with prognosis of patients with congenital heart disease, J. Int. Med. Res. 48 (3) (2020), 300060519884500.
[29] A. Frogoudaki, C. Andreou, J. Parissis, C. Maniotis, M. Nikolaou, I. Rizos, et al., Clinical and prognostic implications of plasma NGAL and NT-proBNP in adult patients with congenital heart disease, Int. J. Cardiol. 177 (3) (2014) 1026–1030.
[30] L.W. Geenen, V.J.M. Baggen, A.E. van den Bosch, J.A. Eindhoven, R.M. Kauling, J.A.A.E. Cuypers, et al., Prognostic value of serial high-sensitivity troponin T measurements in adults with congenital heart disease, Can. J. Cardiol. 36 (9) (2020) 1516–1524.
[31] L.W. Geenen, V.J.M. Baggen, A.E. van den Bosch, J.A. Eindhoven, R.M. Kauling, J.A.A.E. Cuypers, et al., Prognostic value of C-reactive protein in adults with congenital heart disease, Heart 107 (6) (2020) 474–481.
[32] L.W. Geenen, A.R. Opotowsky, C. Lachtrupp, V.J.M. Baggen, S. Brainard, M. J. Landzberg, et al., Tuning and external validation of an adult congenital heart disease risk prediction model, Eur. Heart J. Qual. Care Clin. Outcomes 8 (1) (2022) 70–78.
[33] G. Giannakoulas, K. Dimopoulos, A.P. Bolger, E.L. Tay, R. Inuzuka, E. Bedard, et al., Usefulness of natriuretic peptide levels to predict mortality in adults with congenital heart disease, Am. J. Cardiol. 105 (6) (2010) 869–873.
[34] S. Haberger, M. Hauser, S.L. Braun, T. Schuster, P. Ewert, N. Nagdyman, et al., Prognostic value of plasma B-type natriuretic peptide in the long-term follow-up of patients with transposition of the great arteries with morphologic right systemic ventricle after atrial switch operation, Circ. J. Off. J. Japan. Circ. Soc. 79 (12) (2015) 2677–2681.
[35] B.A. Hoffmann, M. Rybczynski, T. Rostock, H. Servatius, I. Drewitz, D. Steven, et al., Prospective risk stratification of sudden cardiac death in Marfan's syndrome, Int. J. Cardiol. 167 (6) (2013) 2539–2545.
[36] J.Z. Hu, Y.H. Zhang, W. Zhang, J. Liu, P. Peng, A risk prediction model of serious adverse events after cardiac catheterization for Chinese adults patients with moderate and severe congenital heart disease, Rev. Cardiovasc. Med. 23 (12) (2022).
[37] K. Inai, T. Nakanishi, M. Nakazawa, Clinical correlation and prognostic predictive value of neurohumoral factors in patients late after the Fontan operation, Am. Heart J. 150 (3) (2005) 588–594.
[38] M.A. Kampman, A. Balci, D.J. van Veldhuisen, A.P. van Dijk, J.W. Roos-Hesselink, K.M. Sollie-Szarynska, et al., N-terminal pro-B-type natriuretic peptide predicts cardiovascular complications in pregnant women with congenital heart disease, Eur. Heart J. 35 (11) (2014) 708–715.
[39] E. Kowalik, A. Klisiewicz, M. Kowalski, J. Rybicka, R. Baranowski, E.K. Biernacka, P. Hoffman, High-sensitive cardiac troponin T and systemic right ventricular area predict outcomes in adults with congenitally corrected transposition, Can. J. Cardiol. 34 (9) (2018) 1129–1136.
[40] C.L. Lachtrupp, A.M. Valente, M. Gurvitz, M.J. Landzberg, S.B. Brainard, F. M. Wu, et al., Associations between clinical outcomes and a recently proposed adult congenital heart disease anatomic and physiological classification system, J. Am. Heart Assoc. 10 (18) (2021).
[41] A. Lammers, H. Kaemmerer, R. Hollweck, R. Schneider, P. Barthel, S. Braun, et al., Impaired cardiac autonomic nervous activity predicts sudden cardiac death in patients with operated and unoperated congenital cardiac disease, J. Thorac. Cardiovasc. Surg. 132 (3) (2006) 647–655.
[42] M. Laqqan, C. Schwaighofer, S. Graeber, T. Raedle-Hurst, Predictive value of soluble ST2 in adolescent and adult patients with complex congenital heart disease, PLoS One 13 (8) (2018) e0202406.
[43] M. Lipczyńska, P. Szymański, O. Trojnarska, L. Tomkiewicz-Pająk, B. Pietrzak, A. Klisiewicz, et al., Pregnancy in women with complete transposition of the great arteries following the atrial switch procedure. A study from three of the largest Adult Congenital Heart Disease centers in Poland, J. Matern. Fetal Neonatal Med. 30 (5) (2017) 563–567.
[44] A.M. Lubert, T. Alsaied, J.J. Palermo, N. Anwar, E.M. Urbina, N.M. Brown, et al., Fontan-associated dyslipidemia, J. Am. Heart Assoc. 10 (7) (2021) e019578.
[45] E. Martínez-Quintana, H. Estupiñán-León, M. Riaño-Ruiz, F. Rodríguez-González, A. Tugores, Red blood cell distribution width in addition to N-terminal prohormone of B-type natriuretic peptide concentration improves assessment of risk of cardiovascular events in adult patients with congenital heart disease, Arch. Cardiovasc. Dis. 113 (10) (2020) 607–616.
[46] S.J. Maurer, V. Habdank, J. Hörer, P. Ewert, O. Tutarel, NT-proBNP is a predictor of mortality in adults with pulmonary arterial hypertension associated with congenital heart disease, J. Clin. Med. 12 (9) (2023) 3101.
[47] S.J. Maurer, K. Stockemann, C. Pujol, J. Horer, P. Ewert, O. Tutarel, Pulmonary arterial hypertension associated with congenital heart disease in adults over the age of 40 years, J. Clin. Med. 9 (12) (2020).
[48] S.L. Meyer, D. Wolff, F.S. Ridderbos, G. Eshuis, H. Hillege, T.P. Willems, et al., GDF-15 (growth differentiation factor 15) is associated with hospitalization and mortality in patients with a Fontan circulation, J. Am. Heart Assoc. 9 (10) (2020) e015521.
[49] P. Moceri, K. Dimopoulos, E. Liodakis, I. Germanakis, A. Kempny, G.P. Diller, et al., Echocardiographic predictors of outcome in Eisenmenger syndrome, Circulation 126 (12) (2012) 1461–1468.
[50] H. Ohuchi, Y. Hayama, K. Nakajima, K. Kurosaki, I. Shiraishi, M. Nakai, Incidence, predictors, and mortality in patients with liver cancer after fontan operation, J. Am. Heart Assoc. 10 (4) (2021) 1–12.
[51] H. Ohuchi, H. Ikado, K. Noritake, A. Miyazaki, K. Yasuda, O. Yamada, Impact of central venous pressure on cardiorenal interactions in adult patients with congenital heart disease after biventricular repair, Congenit. Heart Dis. 8 (2) (2013) 103–110.
[52] H. Ohuchi, J. Negishi, Y. Hayama, A. Miyazaki, I. Shiraishi, H. Ichikawa, Renal resistive index reflects Fontan pathophysiology and predicts mortality, Heart 103 (20) (2017) 1631–1637.
[53] H. Ohuchi, J. Negishi, Y. Hayama, O. Sasaki, Y. Taniguchi, K. Noritake, et al., Hyperuricemia reflects global Fontan pathophysiology and associates with morbidity and mortality in patients after the Fontan operation, Int. J. Cardiol. 184 (Journal Article) (2015) 623–630.
[54] H. Ohuchi, J. Negishi, H. Miike, Y. Toyoshima, H. Morimoto, M. Fukuyama, et al., Positive pediatric exercise capacity trajectory predicts better adult Fontan physiology rationale for early establishment of exercise habits, Int. J. Cardiol. 274 (2019) 80–87.
[55] H. Ohuchi, J. Negishi, A. Miyake, H. Sakaguchi, A. Miyazaki, O. Yamada, Long-term prognostic value of cardiac autonomic nervous activity in postoperative patients with congenital heart disease, Int. J. Cardiol. 151 (3) (2011) 296–302.
[56] H. Ohuchi, J. Negishi, S. Ono, A. Miyake, N. Toyota, W. Tamaki, et al., Hyponatremia and its association with the neurohormonal activity and adverse clinical events in children and young adult patients after the Fontan operation, Congenit. Heart Dis. 6 (4) (2011) 304–312.
[57] D.M. Parker, A.D. Everett, M.E. Stabler, M.L. Jacobs, J.P. Jacobs, L. Vricella, et al., ST2 predicts risk of unplanned readmission within 1 year after pediatric congenital heart surgery, Ann. Thorac. Surg. 110 (6) (2020) 2070–2075.
[58] J.R. Popelova, K. Kotaska, M. Tomkova, J. Tomek, Usefulness of N-terminal pro-brain natriuretic peptide to predict mortality in adults with congenital heart disease, Am. J. Cardiol. 116 (9) (2015) 1425–1430.
[59] J.R. Popelova, M. Tomkova, J. Tomek, NT-proBNP predicts mortality in adults with transposition of the great arteries late after Mustard or Senning correction, Congenit. Heart Dis. 12 (4) (2017) 448–457.
[60] M. Radman, R.L. Keller, P. Oishi, S.A. Datar, K. Wellnitz, A. Azakie, et al., Preoperative B-type natriuretic peptide levels are associated with outcome after total cavopulmonary connection (Fontan), J. Thorac. Cardiovasc. Surg. 148 (1) (2014) 212–219.
[61] T. Raedle-Hurst, M. Mueller, A. Meinitzer, W. Maerz, T. Dschietzig, Homoarginine-A prognostic indicator in adolescents and adults with complex congenital heart disease? PLoS One 12 (9) (2017) e0184333.
[62] L.C. Reardon, R.J. Williams, L.S. Houser, P.D. Miner, J.S. Child, J.A. Aboulhosn, Usefulness of serum brain natriuretic peptide to predict adverse events in patients with the Eisenmenger syndrome, Am. J. Cardiol. 110 (10) (2012) 1523–1526.
[63] M. Sato, K. Inai, M. Shimizu, H. Sugiyama, T. Nakanishi, Bioelectrical impedance analysis in the management of heart failure in adult patients with congenital heart disease, Congenit. Heart Dis. 14 (2) (2019) 167–175.
[64] M. Schneider, M. Moser, V. Dannenberg, R. Mangold, R. Schonbauer, C. Hengstenberg, H. Gabriel, QRS duration and outcome late after repair of tetralogy of Fallot: neurohormonal activation differentiates between mechanical and electrical dyssynchrony, Congenit. Heart Dis. 15 (1) (2020) 51–58.
[65] M.J. Schuuring, A.C. van Riel, J.C. Vis, M.G. Duffels, J.P. van Straalen, S. M. Boekholdt, et al., High-sensitivity troponin T is associated with poor outcome in adults with pulmonary arterial hypertension due to congenital heart disease, Congenit. Heart Dis. 8 (6) (2013) 520–526.
[66] A. Van De Bruaene, L. Meier, W. Droogne, P. De Meester, E. Troost, M. Gewillig, W. Budts, Management of acute heart failure in adult patients with congenital heart disease, Heart Fail. Rev. 23 (1) (2018) 1–14.
[67] E. van den Bosch, S.S.M. Bossers, V.P. Kamphuis, E. Boersma, J. Roos-Hesselink, J.M.P.J. Breur, et al., Associations between blood biomarkers, cardiac function,

and adverse outcome in a young Fontan cohort, J. Am. Heart Assoc. 10 (5) (2021) e015022.
[68] E. Van Den Bosch, W.J. Van Genuchten, S.E. Luijnenburg, N. Duppen, V. P. Kamphuis, J.W. Roos-Hesselink, et al., Associations between blood biomarkers, cardiac function and adverse outcome in a young tetralogy of Fallot cohort, Int. J. Cardiol. 361 (2022) 31–37.
[69] A.C. van Dissel, I.M. Blok, A.H. Zwinderman, A.P.J. van Dijk, A.L. Duijnhouwer, R.J. de Winter, et al., Prognostic value of multiple repeated biomarkers in pulmonary arterial hypertension associated with congenital heart disease, Eur. J. Heart Fail. 21 (2) (2019) 249–251.
[70] M. Westhoff-Bleck, F. Kornau, A. Haghikia, A. Horke, H. Bertram, J. Treptau, et al., NT-proBNP indicates left ventricular impairment and adverse clinical outcome in patients with tetralogy of fallot and pulmonary regurgitation, Can. J. Cardiol. 32 (10) (2016).
[71] M. Westhoff-Bleck, E. Podewski, O. Tutarel, D. Wenzel, C. Cappello, H. Bertram, et al., Prognostic value of NT-proBNP in patients with systemic morphological right ventricles: a single-centre experience, Int. J. Cardiol. 169 (6) (2013) 433–438.
[72] L. Willinger, L. Brudy, A.L. Häcker, M. Meyer, A. Hager, R. Oberhoffer-Fritz, et al., High-sensitive troponin T and N-terminal pro-B-type natriuretic peptide independently predict survival and cardiac-related events in adults with congenital heart disease, Eur. J. Cardiovasc. Nurs. 23 (1) (2024) 55–61. PMID: 36883916.
[73] R. Zhang, J. Gong, S. Wang, L. Shen, Y. Xie, X. Li, Relationship between serum B7-H3 levels and prognosis of congenital heart disease in children, Pediatr. Cardiol. 40 (1) (2019) 177–181.
[74] Y. Mori, Y. Nakashima, S. Kaneko, N. Inoue, T. Murakami, Risk factors for cardiac adverse events in infants and children with complex heart disease scheduled for bi-ventricular repair: prognostic value of pre-operative B-type natriuretic peptide and high-sensitivity troponin T, Pediatr. Cardiol. 41 (8) (2020) 1756–1765.
[75] G.E. Assenza, D.A. Graham, M.J. Landzberg, A.M. Valente, M.N. Singh, A. Bashir, et al., MELD-XI score and cardiac mortality or transplantation in patients after Fontan surgery, Heart 99 (7) (2013) 491–496.
[76] R. Baptista, C. Marques, S. Catarino, F.J. Enguita, M.C. Costa, P. Matafome, et al., MicroRNA-424(322) as a new marker of disease progression in pulmonary arterial hypertension and its role in right ventricular hypertrophy by targeting SMURF1, Cardiovasc. Res. 114 (1) (2018) 53–64.
[77] I.M. Blok, A.C. van Riel, M.J. Schuuring, R.H. de Bruin-Bon, A.P. van Dijk, E. S. Hoendermis, et al., The role of cystatin C as a biomarker for prognosis in pulmonary arterial hypertension due to congenital heart disease, Int. J. Cardiol. 209 (2016) 242–247.
[78] E.L. Heng, A.P. Bolger, A. Kempny, P.A. Davlouros, S. Davidson, L. Swan, et al., Neurohormonal activation and its relation to outcomes late after repair of tetralogy of Fallot, Heart 101 (6) (2015) 447–454.
[79] R. Konno, S. Tatebe, K. Sugimura, K. Satoh, T. Aoki, M. Miura, et al., Prognostic value of the model for end-stage liver disease excluding INR score (MELD-XI) in patients with adult congenital heart disease, PLoS One 14 (11) (2019) e0225403.
[80] E. Martínez-Quintana, M.M. Sánchez-Matos, H. Estupiñán-León, A. Rojas-Brito, J. M. González-Martín, F. Rodríguez-González, A. Tugores, Malnutrition is independently associated with an increased risk of major cardiovascular events in adult patients with congenital heart disease, Nutr. Metab. Cardiovasc. Dis. 31 (2) (2021) 481–488.
[81] J.L. Rodríguez-Hernández, F. Rodríguez-González, M. Riaño-Ruiz, E. Martínez-Quintana, Risk factors for hyperuricemia in congenital heart disease patients and its relation to cardiovascular death, Congenit. Heart Dis. 13 (5) (2018) 655–662.
[82] G. Scognamiglio, A. Kempny, L.C. Price, R. Alonso-Gonzalez, P. Marino, L. Swan, et al., C-reactive protein in adults with pulmonary arterial hypertension associated with congenital heart disease and its prognostic value, Heart 100 (17) (2014) 1335–1341.
[83] A.R. Opotowsky, F.R. Baraona, F.R. Mc Causland, B. Loukas, E. Landzberg, M. J. Landzberg, et al., Estimated glomerular filtration rate and urine biomarkers in patients with single-ventricle Fontan circulation, Heart 103 (6) (2017) 434–442. Epub 2016 Sep 26. PMID: 27670967; PMCID: PMC5500305.
[84] A. Kempny, G.P. Diller, R. Alonso-Gonzalez, A. Uebing, I. Rafiq, W. Li, et al., Hypoalbuminaemia predicts outcome in adult patients with congenital heart disease, Heart 101 (9) (2015) 699–705.
[85] K. Miyamoto, D. Takeuchi, K. Inai, T. Shinohara, T. Nakanishi, Prognostic value of multiple biomarkers for cardiovascular mortality in adult congenital heart disease: comparisons of single-/two-ventricle physiology, and systemic morphologically right/left ventricles, Heart Vessel. 31 (11) (2016) 1834–1847.
[86] A.R. Opotowsky, A.M. Valente, L. Alshawabkeh, S. Cheng, A. Bradley, E.B. Rimm, M.J. Landzberg, Prospective cohort study of C-reactive protein as a predictor of clinical events in adults with congenital heart disease: results of the Boston adult congenital heart disease biobank, Eur. Heart J. 39 (34) (2018) 3253–3261.
[87] M. Abu-Halima, E. Meese, H. Abdul-Khaliq, T. Raedle-Hurst, MicroRNA-183-3p is a predictor of worsening heart failure in adult patients with transposition of the great arteries and a systemic right ventricle, Front. Cardiol. Vasc. Med. 8 (2021) 730364.
[88] G.P. Diller, K. Dimopoulos, C.S. Broberg, M.G. Kaya, U.S. Naghotra, A. Uebing, et al., Presentation, survival prospects, and predictors of death in Eisenmenger syndrome: a combined retrospective and case-control study, Eur. Heart J. 27 (14) (2006) 1737–1742.
[89] E. Martinez-Quintana, A. Barreto-Martin, H. Estupinan-Leon, A. Rojas-Brito, L. Deniz-Deniz, F. Rodriguez-Gonzalez, Proteinuria versus albuminuria in 24-hour urine collection: prevalence and clinical outcome in non-hypoxemic adult patients with congenital heart disease, Am. J. Cardiovasc Dis. 11 (1) (2021) 46–52.
[90] M. Sato, K. Inai, M. Shimizu, H. Sugiyama, T. Nakanishi, Bioelectrical impedance analysis in the management of heart failure in adult patients with congenital heart disease, Congenit. Heart Dis. 14 (2) (2019) 167–175.
[91] S. Rajpal, L. Alshawabkeh, N. Almaddah, C.M. Joyce, K. Shafer, M. Gurvitz, et al., Association of albuminuria with major adverse outcomes in adults with congenital heart disease: results from the Boston Adult Congenital Heart Biobank, JAMA Cardiol. 3 (4) (2018) 308–316.
[92] A. Van De Bruaene, L. Meier, W. Droogne, P. De Meester, E. Troost, M. Gewillig, W. Budts, Management of acute heart failure in adult patients with congenital heart disease, Heart Fail. Rev. 23 (1) (2018) 1–14.
[93] V.J.M. Baggen, A.E. van den Bosch, J.A. Eindhoven, M.E. Menting, M. Witsenburg, J.A.A.E. Cuypers, et al., Prognostic value of galectin-3 in adults with congenital heart disease, Heart 104 (5) (2018) 394–400.
[94] A.A. Frogoudaki, I. Pantelakis, V. Bistola, C. Kroupis, D. Birba, I. Ikonomidis, et al., Global longitudinal strain of the systemic ventricle is correlated with plasma galectin-3 and predicts major cardiovascular events in adult patients with congenital heart disease, Medicina (Kaunas) 56 (6) (2020) 305.
[95] A.R. Opotowsky, F. Baraona, J. Owumi, B. Loukas, M.N. Singh, A.M. Valente, et al., Galectin-3 Is Elevated and Associated With Adverse Outcomes in Patients With Single-Ventricle Fontan Circulation, J. Am. Heart Assoc. 5 (1) (2016) e002706. PMID: 26755550; PMCID: PMC4859390.
[96] N. Saleh, A. Khattab, M. Rizk, S. Salem, H. Abo-Haded, Value of Galectin-3 assay in children with heart failure secondary to congenital heart diseases: a prospective study, BMC Pediatr. 20 (1) (2020) 537–539.
[97] S.N. Chiu, C.W. Lu, M.T. Lin, C.A. Chen, M.H. Wu, J.K. Wang, Pulmonary hypertension in adult congenital heart disease in Asia: a distinctive feature of complex congenital heart disease, J. Am. Heart Assoc. 11 (7) (2022) e022596.
[98] H. Ohuchi, J. Negishi, Y. Hayama, O. Sasaki, Y. Taniguchi, K. Noritake, et al., Hyperuricemia reflects global Fontan pathophysiology and associates with morbidity and mortality in patients after the Fontan operation, Int. J. Cardiol. 184 (2015) 623–630.
[99] T. Yang, Y.J. Sun, C.M. Xiong, W.J. Zeng, X.H. Ni, Z.H. Zhao, et al., Red blood cell distribution width predicts survival in patients with Eisenmenger syndrome, Clin. Chem. Lab. Med. 52 (5) (2014) 743–750.
[100] K. Dimopoulos, G.P. Diller, R. Petraco, E. Koltsida, G. Giannakoulas, E.L. Tay, et al., Hyponatraemia: a strong predictor of mortality in adults with congenital heart disease, Eur. Heart J. 31 (5) (2010) 595–601.
[101] T. Alsaied, M. Possner, A.M. Lubert, A.T. Trout, C. Szugye, J.J. Palermo, et al., Relation of magnetic resonance elastography to Fontan failure and portal hypertension, Am. J. Cardiol. 124 (9) (2019) 1454–1459.
[102] E. Martinez-Quintana, F. Rodriguez-Gonzalez, Thrombocytopenia in congenital heart disease patients, Platelets 26 (5) (2015) 432–436.
[103] T. Mese, B. Guven, M.M. Yilmazer, C. Karadeniz, R. Ozdemir, O. Doksoz, Platelet activation markers in children with congenital heart disease associated with pulmonary arterial hypertension, Congenit. Heart Dis. 13 (4) (2018) 506–511.
[104] F. Buendia Fuentes, P. Jover Pastor, M.A. Arnau Vives, S. Lozano Edo, M. Rodriguez Serrano, J. Aguero, et al., CA125: a new biomarker in patients with Fontan circulation, Rev. Esp. Cardiol. (Engl Ed). 76 (2) (2023) 112–120.
[105] E. Amer, D. El Amrousy, S. Hazaa, A. Zoair, Serum-soluble suppression of tumourigenicity-2 as a biomarker in children with congestive heart failure, Cardiol. Young (2023) 1–6.
[106] Baggen Geenen, Koudstaal Kauling, Boersma Boomars, et al., The prognostic value of soluble ST2 in adults with pulmonary hypertension, J. Clin. Med. 8 (10) (2019) 1517.
[107] D. El Amrousy, E. Zahran, H. El-Serogy, A. Zoair, Plasma growth differentiation factor-15 in children with pulmonary hypertension associated with congenital heart disease: a canary in the mine? Prog. Pediatr. Cardiol. (2020) 59.
[108] Y.M. Law, C.M. Plonka, B. Feingold, Norepinephrine levels in children with single ventricle circulation, Prog. Pediatr. Cardiol. 47 (2017) 58–63.
[109] V.J.M. Baggen, A.E. van den Bosch, R.R. van Kimmenade, J.A. Eindhoven, M. Witsenburg, J.A.A.E. Cuypers, et al., Red cell distribution width in adults with congenital heart disease: a worldwide available and low-cost predictor of cardiovascular events, Int. J. Cardiol. 260 (2018) 60–65.
[110] K. Miyamoto, K. Inai, D. Takeuchi, T. Shinohara, T. Nakanishi, Relationships among red cell distribution width, anemia, and interleukin-6 in adult congenital heart disease, Circ. J. 79 (5) (2015) 1100–1106.
[111] T. Kogiso, T. Sagawa, M. Taniai, E. Shimada, K. Inai, T. Shinohara, K. Tokushige, Risk factors for Fontan-associated hepatocellular carcinoma, PLoS One 17 (6) (2022) e0270230.
[112] A.C. Egbe, W.R. Miranda, J. Dearani, P.S. Kamath, H.M. Connolly, Prognostic role of hepatorenal function indexes in patients with Ebstein anomaly, J. Am. Coll. Cardiol. 76 (25) (2020) 2968–2976.
[113] A.C. Egbe, W.R. Miranda, J.H. Anderson, R.R. Katta, A.Y. Goda, K. Andi, et al., Determinants and prognostic implications of hepatorenal dysfunction in adults with congenital heart disease, Can. J. Cardiol. 38 (11) (2022) 1742–1750.
[114] G.E. Assenza, D.A. Graham, M.J. Landzberg, A.M. Valente, M.N. Singh, A. Bashir, et al., MELD-XI score and cardiac mortality or transplantation in patients after Fontan surgery, Heart 99 (7) (2013) 491–496.
[115] L.W. Geenen, R.W.J. van Grootel, K. Akman, V.J.M. Baggen, M.E. Menting, J. A. Eindhoven, et al., Exploring the prognostic value of novel markers in adults with a systemic right ventricle, J. Am. Heart Assoc. 8 (17) (2019) e013745.
[116] M. Jansen, S. Algul, L.P. Bosman, M. Michels, J. van der Velden, R.A. de Boer, et al., Blood-based biomarkers for the prediction of hypertrophic cardiomyopathy

prognosis: a systematic review and meta-analysis, ESC Heart Fail. 9 (5) (2022) 3418–3434.
[117] A. Piek, W. Du, R.A. de Boer, H.H.W. Sillje, Novel heart failure biomarkers: why do we fail to exploit their potential? Crit. Rev. Clin. Lab. Sci. 55 (4) (2018) 246–263.
[118] I.S. Anand, R. Latini, V.G. Florea, M.A. Kuskowski, T. Rector, S. Masson, et al., Val-HeFT Investigators, C-reactive protein in heart failure: prognostic value and the effect of valsartan, Circulation 112 (10) (2005) 1428–1434. Epub 2005 Aug 29. PMID: 16129801.
[119] J. Danesh, P. Whincup, M. Walker, L. Lennon, A. Thomson, P. Appleby, et al., Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses, BMJ 321 (7255) (2000) 199–204. PMID: 10903648; PMCID: PMC27435.
[120] S. Sanada, D. Hakuno, L.J. Higgins, E.R. Schreiter, A.N. McKenzie, R.T. Lee, IL-33 and ST2 comprise a critical biomechanically induced and cardioprotective signaling system, J. Clin. Invest. 117 (6) (2007) 1538–1549.
[121] C.R. Benedict, B. Shelton, D.E. Johnstone, G. Francis, B. Greenberg, M. Konstam, et al., Prognostic significance of plasma norepinephrine in patients with asymptomatic left ventricular dysfunction, SOLVD Invest. Circulation 94 (4) (1996) 690–697.
[122] J.A. Thomas, B.H. Marks, Plasma norepinephrine in congestive heart failure, Am. J. Cardiol. 27th Ann. Sci. Session Am. Coll. Cardiol. 41 (2) (1978) 233–243.
[123] K. Norozi, R. Buchhorn, A. Yasin, S. Geyer, L. Binder, J.A. Seabrook, A. Wessel, Growth differentiation factor 15: an additional diagnostic tool for the risk stratification of developing heart failure in patients with operated congenital heart defects? Am. Heart J. 162 (1) (2011) 131–135.
[124] I.S. Anand, T. Kempf, T.S. Rector, H. Tapken, T. Allhoff, F. Jantzen, et al., Serial measurement of growth-differentiation factor-15 in heart failure: relation to disease severity and prognosis in the Valsartan Heart Failure Trial, Circulation 122 (14) (2010) 1387–1395.
[125] L. Rochette, G. Dogon, M. Zeller, Y. Cottin, C. Vergely, GDF15 and cardiac cells: current concepts and new insights, Int. J. Mol. Sci. 22 (16) (2021).
[126] F.A. McAlister, J. Ezekowitz, M. Tonelli, P.W. Armstrong, Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study, Circulation 109 (8) (2004) 1004–1009.
[127] C. Orsborne, P.S. Chaggar, S.M. Shaw, S.G. Williams, The renin-angiotensin-aldosterone system in heart failure for the non-specialist: the past, the present and the future, Postgrad. Med. J. 93 (1095) (2017) 29–37.
[128] S.D. Anker, W. Doehner, M. Rauchhaus, R. Sharma, D. Francis, C. Knosalla, et al., Uric acid and survival in chronic heart failure: validation and application in metabolic, functional, and hemodynamic staging, Circulation 107 (15) (2003) 1991–1997.
[129] G. Fanali, A. di Masi, V. Trezza, M. Marino, M. Fasano, P. Ascenzi, Human serum albumin: from bench to bedside, Mol. Asp. Med. 33 (3) (2012) 209–290.
[130] C.E. Ha, N.V. Bhagavan, Novel insights into the pleiotropic effects of human serum albumin in health and disease, Biochim. Biophys. Acta 1830 (12) (2013) 5486–5493.
[131] T.A. McDonagh, M. Metra, M. Adamo, R.S. Gardner, A. Baumbach, M. Bohm, et al., 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure, Eur. Heart J. 42 (36) (2021) 3599–3726.
[132] A. Filusch, E. Giannitsis, H.A. Katus, F.J. Meyer, High-sensitive troponin T: a novel biomarker for prognosis and disease severity in patients with pulmonary arterial hypertension, Clin. Sci. (London, England : 1979) 119 (5) (2010) 207–213.
[133] T. Reichlin, A. Irfan, R. Twerenbold, M. Reiter, W. Hochholzer, H. Burkhalter, et al., Utility of absolute and relative changes in cardiac troponin concentrations in the early diagnosis of acute myocardial infarction, Circulation 124 (2) (2011) 136–145.
[134] A. Torbicki, M. Kurzyna, P. Kuca, A. Fijałkowska, J. Sikora, M. Florczyk, et al., Detectable serum cardiac troponin T as a marker of poor prognosis among patients with chronic precapillary pulmonary hypertension, Circulation 108 (7) (2003) 844–848.
[135] R. Latini, S. Masson, I.S. Anand, E. Missov, M. Carlson, T. Vago, et al., Prognostic value of very low plasma concentrations of troponin T in patients with stable chronic heart failure, Circulation 116 (11) (2007) 1242–1249.
[136] A. Ghorbani, V. Bhambhani, R.H. Christenson, W.C. Meijers, R.A. de Boer, D. Levy, et al., Longitudinal change in galectin-3 and incident cardiovascular outcomes, J. Am. Coll. Cardiol. 72 (25) (2018) 3246–3254.
[137] L.A. Allen, G.M. Felker, M.R. Mehra, J.R. Chiong, S.H. Dunlap, J.K. Ghali, et al., Validation and potential mechanisms of red cell distribution width as a prognostic marker in heart failure, J. Card. Fail. 16 (3) (2010) 230–238.
[138] G.M. Felker, L.A. Allen, S.J. Pocock, L.K. Shaw, J.J. McMurray, M.A. Pfeffer, et al., Red cell distribution width as a novel prognostic marker in heart failure: data from the CHARM Program and the Duke Databank, J. Am. Coll. Cardiol. 50 (1) (2007) 40–47.
[139] D.A. Pascual-Figal, J.C. Bonaque, B. Redondo, C. Caro, S. Manzano-Fernandez, J. Sánchez-Mas, et al., Red blood cell distribution width predicts long-term outcome regardless of anaemia status in acute heart failure patients, Eur. J. Heart Fail. 11 (9) (2009) 840–846.
[140] G. Turcato, E. Zorzi, D. Prati, G. Ricci, A. Bonora, M. Zannoni, et al., Early in-hospital variation of red blood cell distribution width predicts mortality in patients with acute heart failure, Int. J. Cardiol. 243 (Journal Article) (2017) 306–310.
[141] R.R. van Kimmenade, A.A. Mohammed, S. Uthamalingam, P. van der Meer, G. M. Felker, J.L. Januzzi Jr., Red blood cell distribution width and 1-year mortality in acute heart failure, Eur. J. Heart Fail. 12 (2) (2010) 129–136.
[142] H. Baumgartner, J. De Backer, S.V. Babu-Narayan, W. Budts, M. Chessa, G.-P. Diller, et al., 2020 ESC Guidelines for the management of adult congenital heart disease, Eur. Heart J. 42 (6) (2021) 563–645.
[143] J.A. Eindhoven, A.E. Van Den Bosch, P.R. Jansen, E. Boersma, J.W. Roos-Hesselink, The usefulness of brain natriuretic peptide in complex congenital heart disease, J. Am. Coll. Cardiol. 60 (21) (2012) 2140–2149.
[144] A.M.E. Koch, S. Zink, H. Singer, S. Dittrich, B-type natriuretic peptide levels in patients with functionally univentricular hearts after total cavopulmonary connection, Eur. J. Heart Fail. 10 (1) (2008) 60–62.
[145] J.A. Eindhoven, J.W. Roos-Hesselink, A.E. van den Bosch, I. Kardys, J.M. Cheng, J.F. Veenis, et al., High-sensitive troponin-T in adult congenital heart disease, Int. J. Cardiol. 184 (2015) 405–411.
[146] J.M. Kuijpers, I. Vaartjes, J.P. Bokma, J.P. van Melle, G.T. Sieswerda, T. C. Konings, et al., Risk of coronary artery disease in adults with congenital heart disease: a comparison with the general population, Int. J. Cardiol. 304 (2020) 39–42.
[147] R.S. Alipour Symakani, W.J. van Genuchten, L.M. Zandbergen, S. Henry, Y. Taverne, D. Merkus, et al., The right ventricle in tetralogy of Fallot: adaptation to sequential loading, Front. Pediatr. 11 (2023) 1098248.
[148] A. Biernacka, N.G. Frangogiannis, Aging and cardiac fibrosis, Aging Dis. 2 (2) (2011) 158–173.
[149] S. Cullen, D. Shore, A. Redington, Characterization of right ventricular diastolic performance after complete repair of tetralogy of Fallot. Restrictive physiology predicts slow postoperative recovery, Circulation 91 (6) (1995) 1782–1789.
[150] H. Senzaki, S. Masutani, H. Ishido, M. Taketazu, T. Kobayashi, N. Sasaki, et al., Cardiac rest and reserve function in patients with Fontan circulation, J. Am. Coll. Cardiol. 47 (12) (2006) 2528–2535.
[151] B.R. Don, G. Kaysen, Serum albumin: relationship to inflammation and nutrition, Semin. Dial. 17 (6) (2004) 432–437.
[152] R. Sharma, A.P. Bolger, W. Li, P.A. Davlouros, H.D. Volk, P.A. Poole-Wilson, et al., Elevated circulating levels of inflammatory cytokines and bacterial endotoxin in adults with congenital heart disease, Am. J. Cardiol. 92 (2) (2003) 188–193.
[153] P.J. Vinholt, A.M. Hvas, H. Frederiksen, L. Bathum, M.K. Jørgensen, M. Nybo, Platelet count is associated with cardiovascular disease, cancer and mortality: a population-based cohort study, Thromb. Res. 148 (Journal Article) (2016) 136–142.
[154] D. Gregg, P.J. Goldschmidt-Clermont, Cardiology patient page. Platelets and cardiovascular disease, Circulation 108 (13) (2003) 88.
[155] M. Peck-Radosavljevic, Thrombocytopenia in chronic liver disease, Liver Int. 37 (6) (2017) 778–793. Epub 2016 Dec 27. PMID: 27860293.
[156] A.C. Egbe, W.R. Miranda, J. Dearani, P.S. Kamath, H.M. Connolly, Prognostic role of hepatorenal function indexes in patients with Ebstein anomaly, J. Am. Coll. Cardiol. 76 (25) (2020) 2968–2976.
[157] E. Ritmeester, V.A. Veger, J.P.G. van der Ven, G. van Tussenbroek, C.I. van Capelle, F.E.A. Udink Ten Cate, W.A. Helbing, Fontan circulation associated organ abnormalities beyond the heart, lungs, liver, and gut: a systematic review, Front. Cardiovasc. Med. 9 (2022) 826096.
[158] E.M. Leusveld, R.M. Kauling, L.W. Geenen, J.W. Roos-Hesselink, Heart failure in congenital heart disease: management options and clinical challenges, Expert. Rev. Cardiovasc. Ther. 18 (8) (2020) 503–516.
[159] M.T. Gurgoze, L.C. van Vark, S.J. Baart, I. Kardys, K.M. Akkerhuis, O. C. Manintveld, et al., Multimarker analysis of serially measured GDF-15, NT-proBNP, ST2, GAL-3, cTnI, creatinine, and prognosis in acute heart failure, Circ. Heart Fail. 16 (1) (2023) e009526.
[160] L.W. Geenen, V.J.M. Baggen, T. Koudstaal, K.A. Boomars, J.A. Eindhoven, E. Boersma, et al., The prognostic value of various biomarkers in adults with pulmonary hypertension; a multi-biomarker approach, Am. Heart J. 208 (2019) 91–99.
[161] C. McGinn, F.A. Casey, C. Watson, L. Morrison, Paediatric heart failure - understanding the pathophysiology and the current role of cardiac biomarkers in clinical practice, Cardiol. Young 33 (4) (2023) 503–513.
[162] W.C. Meijers, A. Bayes-Genis, A. Mebazaa, J. Bauersachs, J.G.F. Cleland, A.J. S. Coats, et al., Circulating heart failure biomarkers beyond natriuretic peptides: review from the Biomarker Study Group of the Heart Failure Association (HFA), European Society of Cardiology (ESC), Eur. J. Heart Fail. 23 (10) (2021) 1610–1632.
[163] T.R. Fleming, C.E. Garnett, L.S. Conklin, S. Corriol-Rohou, S. Hariharan, D. Hsu, et al., Innovations in Pediatric Therapeutics Development: Principles for the Use of Bridging Biomarkers in Pediatric Extrapolation, Ther. Innov. Regul. Sci. 57 (1) (2023) 109–120. Epub 2022 Sep 3. PMID: 36057747; PMCID: PMC9755084.
[164] W. Schmitt, H. Rühs, R. Burghaus, C. Diedrich, S. Duwal, T. Eissing, et al., NT-proBNP qualifies as a surrogate for clinical end points in heart failure, Clin. Pharmacol. Therapeut. 110 (2) (2021) 498–507.
[165] D. Bonnet, F. Berger, E. Jokinen, P.F. Kantor, P.E.F. Daubeney, Ivabradine in children with dilated cardiomyopathy and symptomatic chronic heart failure, J. Am. Coll. Cardiol. 70 (10) (2017) 1262–1272.
[166] J. Nunez, R. de la Espriella, P. Rossignol, A.A. Voors, W. Mullens, M. Metra, et al., Congestion in heart failure: a circulating biomarker-based perspective. A review from the Biomarkers Working Group of the Heart Failure Association, European Society of Cardiology, Eur. J. Heart Fail. 24 (10) (2022) 1751–1766.
[167] E. van den Bosch, W.J. van Genuchten, S.E. Luijnenburg, N. Duppen, V. P. Kamphuis, J.W. Roos-Hesselink, et al., Associations between blood biomarkers, cardiac function and adverse outcome in a young tetralogy of Fallot cohort, Int. J. Cardiol. 361 (2022) 31–37. Epub 2022 Apr 26. PMID: 35487320.
[168] J.P.G. van der Ven, E. van den Bosch, V.P. Kamphuis, C. Terol, D. Gnanam, A.J.J. C. Bogers, et al., Functional Echocardiographic and Serum Biomarker Changes

Following Surgical and Percutaneous Atrial Septal Defect Closure in Children, J. Am. Heart Assoc. 11 (16) (2022) e024072. Epub 2022 Aug 5. PMID: 35929457; PMCID: PMC9496284.

[169] L. Adamo, J. Yu, C. Rocha-Resende, A. Javaheri, R.D. Head, D.L. Mann, Proteomic Signatures of Heart Failure in Relation to Left Ventricular Ejection Fraction, J. Am. Coll. Cardiol. 76 (17) (2020) 1982–1994. PMID: 33092734; PMCID: PMC7584807.

[170] A. Bayes-Genis, A. Aimo, P. Jhund, M. Richards, R.A. de Boer, H. Arfsten, et al., Biomarkers in heart failure clinical trials. A review from the Biomarkers Working Group of the Heart Failure Association of the European Society of Cardiology, Eur. J. Heart Fail. 24 (10) (2022) 1767–1777. Epub 2022 Sep 20. Erratum in: Eur J Heart Fail. 2023 Mar;25(3):443. doi: 10.1002/ejhf.2789. PMID: 36073112.

[171] E. van den Bosch, W.J. van Genuchten, S.E. Luijnenburg, N. Duppen, V. P. Kamphuis, J.W. Roos-Hesselink, et al., Associations between blood biomarkers, cardiac function and adverse outcome in a young tetralogy of Fallot cohort, Int. J. Cardiol. 361 (2022) 31–37.

[172] Wouter J. van Genuchten, Eva van den Bosch, Saskia E. Luijnenburg, Vivian P. Kamphuis, Jolien W. Roos-Hesselink, Beatrijs Bartelds, et al., Changes in blood biomarkers correlate with changes in cardiac size and function in patients with tetralogy of Fallot, Int. J. Cardiol. Congenit. Heart Dis. 17 (2024) 100522. ISSN 2666-6685 (https://www.sciencedirect.com/science/article/pii/S2666668524000314).