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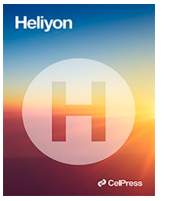

Research article

Fibroblast growth factor 23 during septic shock and myocardial injury in ICU patients

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A B S T R A C T

Objective: Fibroblast growth factor 23 (FGF23) has been recognized as an important biomarker of cardiovascular disease and is closely related to inflammation over the past decade. This study aimed to assess the relationship between FGF23 and myocardial injury in patients with sepsis.
Methods: We sequentially measured serum FGF23, Klotho, biomarkers of inflammation (CRP, IL-6 and WBC), myocardial injury (cTnI and N-terminal B-type natriuretic peptide) and sepsis (procalcitonin) at peak of intercurrent septic shock and after complete resolution or before death in a series of 29 patients with septic shock. 29 healthy adults without infections were used as controls.
Results: There was a difference in serum FGF23 level between patients with septic shock and healthy adults ($p < 0.0001$), and the peak level of FGF23 in septic shock in the survivor group was higher than that after complete remission ($p < 0.0001$). No statistical difference was found in the level of FGF23 before and after treatment in the death group ($p = 0.0947$). At the peak of septic shock, FGF23 was significantly correlated with inflammatory markers, CRP ($r = 0.8063$, $p < 0.0001$), PCT ($r = 0.6091$, $p = 0.0005$) and WBC ($r = 0.8312$, $p < 0.0001$), while the correlation with IL-6 was not statistically significant ($r = 0.0098$, $p = 0.9598$). At the same time, it was found that FGF23 was significantly correlated with myocardial injury markers, cTNI ($r = 0.8475$, $p < 0.0001$) and NTproBNP ($r = 0.8505$, $p < 0.0001$). Nevertheless, FGF23 and klotho are not correlated ($r = 0.2609$, $p = 0.1717$).
Conclusion: In conclusion, in patients with septic shock and myocardial injury, the exacerbation of inflammation in the septic process was accompanied by a abnormal increase of circulating FGF23 level. FGF23 also subsided after the improvement of inflammation, and the opposite was true for patients who did not survive. The up-regulation of FGF23 may be involved in the response of patients to septic shocks, and it is also speculated that FGF23 is involved in the myocardial injury of septic shock.

1. Introduction

Sepsis is defined as a serious life-threatening organ dysfunction, which is caused by the maladjustment of host response to infection, which has a worldwide mortality rate of 10% [1]. Myocardial injury is a common complication of sepsis. Research indicates that at least 40% of patients with sepsis will suffer from myocardial injury [2]. Recent studies have found that its pathogenesis includes inflammatory reaction disorder, oxidative stress, calcium regulation disorder, autonomic nervous system disorder, autophagy damage, apoptosis damage, mitochondrial dysfunction and endothelial dysfunction [3], however, the precise mechanisms remain incompletely understood. Researchers are keen to identify proactive methods to prevent myocardial injury in sepsis at an earlier stage.

Fibroblast growth factor 23 (FGF23) belongs to the overall protein family that regulates cell proliferation, and is a hormone mainly secreted and synthesized by osteocytes and osteoblasts [4]. In essence, FGF23 regulates the homeostasis of phosphorus in the body by regulating the reabsorption of phosphate by the kidney and parathyroid gland, reducing the production of parathyroid hormone and

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down-regulating the synthesis of active vitamin D [5]. In addition, previous studies have found that FGF23 not only plays a role in phosphate regulation, but also shows adverse effects on myocardial cells. FGF23 seems to be a positive predictor of sepsis mortality and cardiovascular complications [6].

In this study, we examined the relationship between plasma FGF23 concentration and the risk of sepsis death in study participants, and observed the direct relationship between and myocardial injury during sepsis. We speculate that the higher circulating concentration is related to the increased mortality of sepsis and myocardial injury.

2. Materials and methods

2.1. Study protocols and population selection

This is a prospective observational study conducted from October 2021 to October 2022 in the Department of Intensive Care Unit of a third-Grade Class-A Hospital (Hangzhou Red Cross Hospital, Zhejiang, China). All patients diagnosed with septic shock [7] accompanied by myocardial injury were included. The study protocol involving human participants was reviewed and approved by Medical Ethics Committee of Hangzhou Red Cross Hospital (No. 2021-245) and was performed in accordance with the Declaration of Helsinki. In total, The patients/participants provided their written informed consent to participate in this study.

The inclusion criteria were as follows.

- I diagnosis of septic shock according to the sepsis-3 definition [7] on admission to the ICU;
- II cardiac troponin I (cTnI) levels >0.04 ng/mL (detected by the PATHFAST chemiluminescence immunoassay; Hangzhou Red Cross Hospital, Zhejiang, China) on admission to the ICU [8];
- III age ≥18 years.

The exclusion criteria were as follows: Patients with a history of myocardial disease, valvular heart disease, congenital heart disease, tumor or autoimmune disease, and who have not received acute coronary syndrome, chest compression, defibrillation, direct current cardioversion, severe heart failure or cardiac surgery, and pregnant women in the past two weeks.

29 healthy adults without infections were used as controls.

2.2. Data collection and grouping

Data on age, sex, medical history of basic illness, laboratory tests, and causes of septic shock infection were collected. The patients' vital signs were obtained during the diagnosis of septic shock, including sex, age, BMI, systolic blood pressure, and diastolic blood pressure. We also collected blood biochemical indicators through the medical record system (white blood cell (WBC), Haemoglobin, and levels of creatinine, Serum calcium ion, serum phosphorus ion, N-terminal B-type natriuretic peptide (NTproBNP), serum albumin, procalcitonin (PCT), cTnI, and C-reactive protein (CRP)).

Patients were divided into a survival group and a non-survival group based on whether they occurred all-cause mortality within 28 days of admission to the ICU. The control group consisted of 29 healthy adults.

2.3. Enzyme-linked immunosorbent assay (ELISA) tests

Blood samples were immediately collected from both patients and healthy adults meeting the inclusion criteria upon their admission to the ICU under standard conditions. The samples were centrifuged at 3000 g for 10 min at room temperature. Supernatants were stored in aliquots at −80 °C until further use. FGF-23 levels were measured from plasma samples by ELISA (Human FGF23 ELISA Kit, ab267652). Klotho levels were measured from plasma samples by ELISA (Human Klotho ELISA Kit, EA102490). Interleukin 6 (IL-6) levels were measured from plasma samples by ELISA (Human IL-6 ELISA Kit, EHC007.96).

2.4. Statistical analysis

Measurement data conformed to normal distribution were expressed as the mean ± standard deviation (SD). An independent sample *t*-test was used to compare measurement data of the two groups Data that did not conform to a normal distribution are shown by the median (interquartile range, [25th percentile, 75th percentile). Comparison between groups was performed using the rank-sum test. Categorical data are presented as the percentage and the chi-square test was performed for comparisons. Pearson correlation and linear regression were performed to examine the relationship between two parameters. In the longitudinal study, differences between the samples taken at the peak of acute infection and after resolution of this process were analysed by paired *t*-test or Wilcoxon-matched pair's test as appropriate, and the corresponding point estimates were expressed as mean SD. P values < 0.05 were considered statistically significant. All statistical analyses were performed u1sing IBM SPSS statistics, version 22.0 (IBM Corp., Armonk, NY). Graphs were created in GraphPad Prism(version 7, GraphPad Prism Software, Inc.).

3. Results

3.1. Baseline patient characteristics

The main clinical characteristics of the 29 patients with acute septic shock enrolled in this study are presented in Table 1. The cause of sepsis was a broncho-pulmonary or urinary infection in 24 patients, bacterial contamination of an intravenous cannula in 5. Comorbidities in these patients included diabetes mellitus in 18 patients, coronary heart disease and chronic heart failure in 11 patients, chronic pulmonary obstructive disease in 16 patients. 19 patients had an uneventful recovery from septic shock. 10 patients failed to survive. All patients were treated according to conventional treatment strategy [9] during hospitalization.

3.2. Inflammatory biomarkers at the peak of sepsis and after regression or death

With regard to the changes of serum inflammatory biomarkers (IL-6, CRP, PCT and WBC) in septic shock patients. The sepsis peak level of various inflammatory indicators in the survival group was significantly higher than that after complete remission (All $p < 0.0001$). However, in the death group, only the peak level of PCT sepsis was statistically different from that before death ($p = 0.044$), other inflammatory biomarkers, IL-6, CRP and WBC were not statistically different ($p = 0.222$, $p = 0.344$, $p = 0.062$) (Table 2).

3.3. FGF23 and biomarkers of inflammation and myocardial injury during septic shock

In order to determine the increase of circulating FGF23 level in patients with sepsis, we tested healthy adults (Fig. 1A a). There was a significant difference in FGF23 levels between the peak of survivors and those after complete remission in patients with sepsis (Fig. 1A b). There was no difference in FGF23 levels between the peak of non-survivors and those before death (Fig. 1A c).

In order to find the role of FGF23 in septic shock, the following observations were made. In our analysis, including 29 patients with septic shock, FGF23 was significantly correlated with inflammatory markers, CRP ($r = 0.8063$, $p < 0.0001$), PCT ($r = 0.6091$, $p = 0.0005$) and WBC ($r = 0.8312$, $p < 0.0001$), while the correlation with IL-6 was not statistically significant ($r = 0.0098$, $p = 0.9598$). At the same time, it was found that FGF23 was significantly correlated with myocardial injury markers, cTNI ($r = 0.8475$, $p < 0.0001$) and NTproBNP ($r = 0.8505$, $p < 0.0001$) (Fig. 1B).

3.4. Klotho and biomarkers of inflammation and myocardial injury during septic shock

In order to determine the increase of circulating klotho level in patients with sepsis, we tested healthy adults (Fig. 2A a). In addition, there was no difference between the peak value of klotho level between survivors and non-survivors in patients with sepsis and after complete remission or before death (Fig. 2A b c).

Klotho was directly related with biomarkers of inflammation and myocardial injury,WBC ($r = 0.3867$, $p = 0.0383$), IL-6 ($r = 0.1888$, $p < 0.0082$), NTproBNP ($r = 0.4814$, $p < 0.0082$), and cTNI ($r = 0.4467$, $p = 0.0151$), but was unrelated with other biomarkers of inflammation, CRP ($r = 0.1343$, $p < 0.4875$), PCT ($r = 0.3156$, $p < 0.0954$) (Fig. 2B).

3.5. FGF23 and klotho

We guessed whether the relationship between FGF23 and myocardial injury during septic shock passes through klotho. Nevertheless, FGF23 and klotho were not correlated ($r = 0.2609$, $p = 0.1717$) (Fig. 3).

Table 1
Clinical characteristics and laboratory data of the 29 patients with sepsis at admission.

	Patients (n = 29)
Age (years)	84.07 ± 13.07
Gender (male)	23 (79.31%)
BMI (kg/m2)	21.84 ± 1.45
Heart Rate (beats/min)	107.45 ± 25.46
Systolic pressure (mmHg)	106.55 ± 9.96
Diastolic pressure (mmHg)	53.03 ± 6.71
Haemoglobin (g/dl)	84.79 ± 20.21
Calcium (mg/dL)	2.06 ± 0.27
Phosphate (mg/dL)	0.79 ± 0.32
Albumin (g/dL)	27.19 ± 3.84
cTNI (ng/L)	0.62 ± 0.33
NTproBNP (pg/ml)	5008.56 ± 2730.61

Data are expressed as mean ± SD, geometric mean ± SD or number and percentage frequency, as appropriate. SD, standard deviation; BMI, body mass index; cTNI, cardiac troponin I; NTproBNP, N-terminal B-type natriuretic peptide.

Table 2
Levels of IL-6, CRP, PCT and WBC at peak sepsis and after the resolution or death.

	Peak of Infection	Resolution of infection OR Death	P
Survival group			
IL-6 (pg/ml)	93.33 ± 39.59	14.75 ± 7.37	<0.0001
CRP (mg/L)	117.62 ± 37.29	21.85 ± 13.17	<0.0001
PCT (ng/mL)	16.47 ± 13.68	1.85 ± 0.96	<0.0001
WBC (10^9/L)	16.57 ± 4.65	8.61 ± 2.50	<0.0001
Death group			
IL-6 (pg/ml)	68.50 ± 30.08	53.87 ± 24.03	0.222
CRP (mg/L)	137.32 ± 52.84	126.14 ± 58.59	0.344
PCT (ng/mL)	25.77 ± 9.85	17.94 ± 9.07	0.044
WBC (10^9/L)	18.28 ± 4.33	15.81 ± 5.07	0.062

Data are expressed as mean ± SD or geometric mean ± SD, as appropriate. IL-6, interleukin 6; CRP, C-reactive protein; PCT, procalcitonin; WBC, white blood cell.

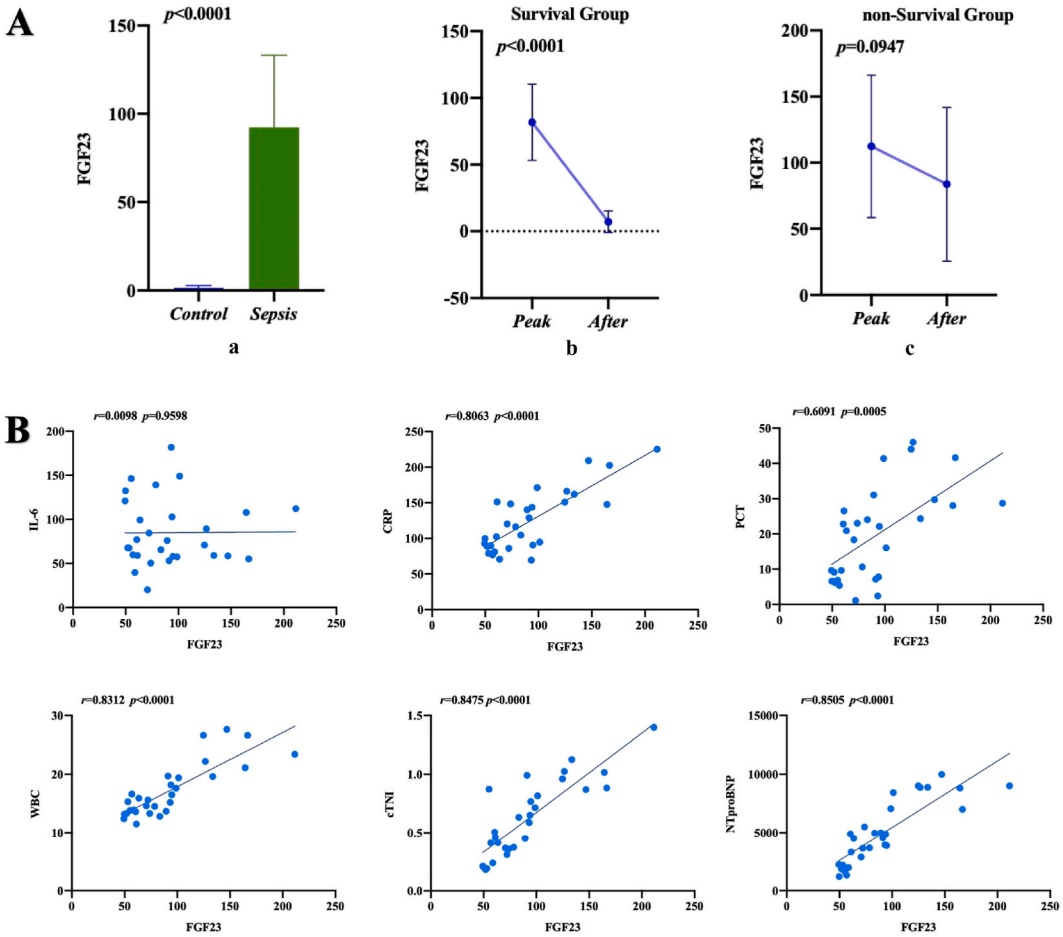

Fig. 1. **A** a: Comparison of FGF23 (pg/mL) between patients with sepsis and healthy people. b: Changes in FGF23 (pg/mL) at peak sepsis and after resolution of sepsis. c: Changes of FGF23 (pg/mL) at peak sepsis and death. **B** Relationship between FGF23 with biomarkers of inflammation (IL-6, CRP, PCT and WBC) and markers of cardiac injury (cTNI and NTproBNP) at peak infection of infection. Data are Pearson Product moment correlation coefficients and P values. IL-6, Interleukin 6; CRP, C-reactive protein; PCT, procalcitonin; WBC, white blood cell; cTNI, cardiac troponin I; NTproBNP, N-terminal B-type natriuretic peptide.

4. Discussion

In this study, the circulating FGF23 level in patients with septic shock was higher at the peak of infection than the stable level after complete remission. In general, these findings suggested that the up-regulation of FGF23 may participate in the regulation of myocardial injury response in patients with septic shock.

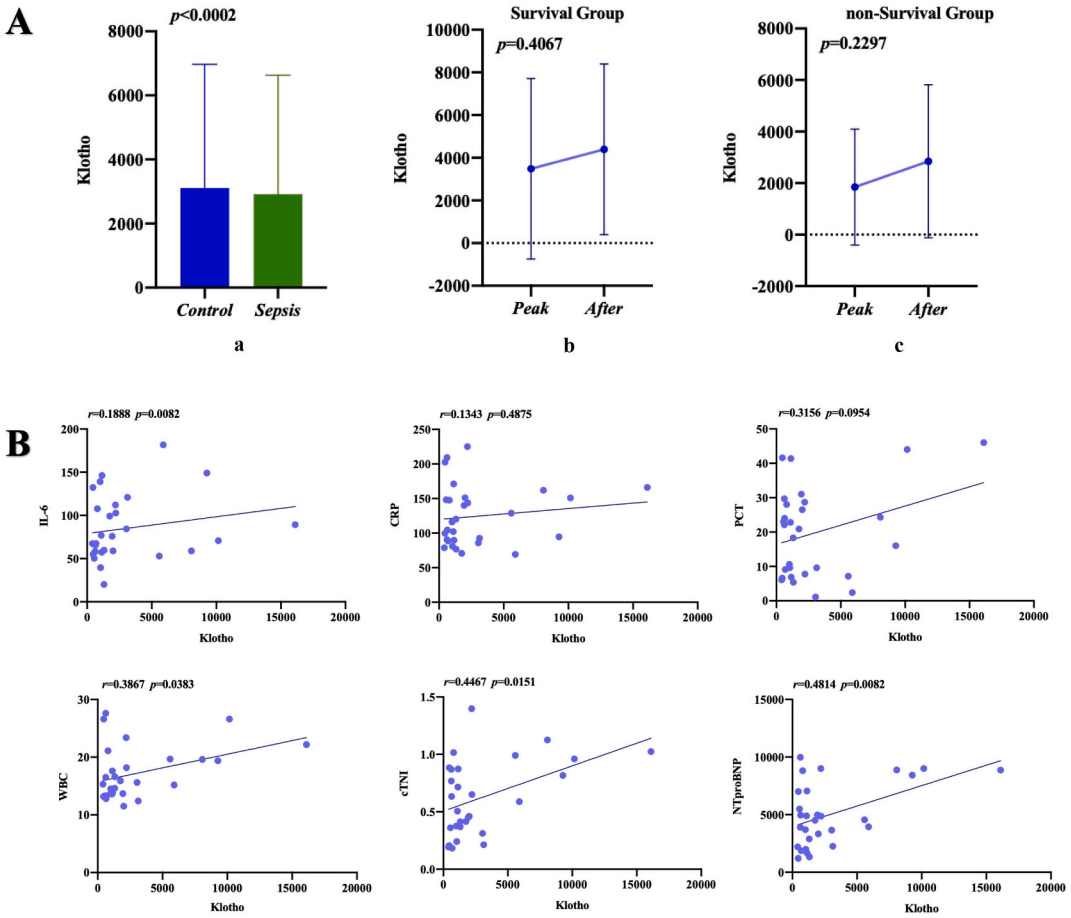

Fig. 2. **A** a: Comparison of klotho (pg/mL) between patients with sepsis and healthy people. b: Changes in klotho (pg/mL) at peak sepsis and after resolution of sepsis. c: Changes of klotho (pg/mL) at peak sepsis and death. **B** Relationship between klotho with biomarkers of inflammation (IL-6, CRP, PCT and WBC) and markers of cardiac injury (cTNI and NTproBNP) and FGF23 at peak infection of infection. Data are Pearson Product moment correlation coefficients and P values. IL-6, Interleukin 6; CRP, C-reactive protein; PCT, procalcitonin; WBC, white blood cell; cTNI, cardiac troponin I; NTproBNP, N-terminal B-type natriuretic peptide.

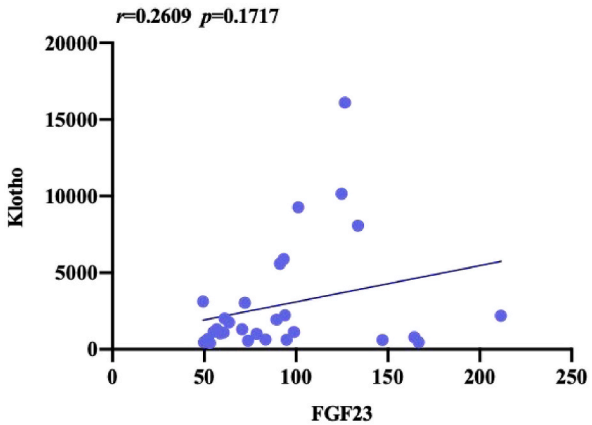

Fig. 3. Relationship between klotho with FGF23 at peak infection of infection. Data are Pearson Product moment correlation coefficients and P values.

Our study confirmed that the level of serum FGF23 in patients with septic shock in the acute phase was significantly higher than that in the remission phase, which was consistent with the changes of serum WBC, CRP, PCT and IL-6. Inflammation is associated with an increase in FGF23 in many different diseases, such as sepsis and autoimmune diseases [10]. There is a positive feedback circuit between inflammation and FGF23. FGF23 induces more FGF23 production by stimulating the secretion of pro-inflammatory cytokines. The elevated level of FGF23 in mice resulted in the elevated levels of CRP and IL-6 in liver and serum [11]. In inflammatory state, inflammatory cytokines directly induce the production of FGF23 in bone and osteoblast/osteocyte cell lines. Sepsis patients often experience transient hypophosphataemia, suggesting the regulation of FGF23 levels by pro-inflammatory factors. Researchers used the osteocyte-like cell line IDG-SW3 to investigate the effect of pro-inflammatory stimuli on FGF23 production. In differentiated IDG-SW3 cultures, basal FGF23 mRNA was dose-dependently up-regulated by pro-inflammatory cytokines tumor necrosis factor (TNF), IL-1β and tumor necrosis factor-like weak inducer of apoptosis (TWEAK), and bacterial LPS. Similar effects were observed in human bone samples. Results demonstrate that pro-inflammatory stimuli are capable of increasing osteocyte secretion of FGF23 [12].

FGF23 has been proved to inhibit the production of CYP27B1. Increasing the concentration of FGF23 can reduce $1,25(OH)_2D$-dependent synthesis of cathelicin, resist a variety of bacteria, viruses and fungi, destroy biofilm and promote phagocytosis, which is an important antimicrobial peptide [13]. In addition, FGF23 is also able to inhibit the synthesis of antibacterial molecule LL37 in peripheral blood monocytes, and it is speculated that FGF23 may significantly regulate the immune inflammatory response in renal failure through this pathway [14]. In a small prospective cohort study, 30 hospitalized adults and 30 non-hospitalized healthy adults were included. The results showed that the level of FGF23 was positively correlated with the severity of sepsis [15].

Traditionally, FGF23 is believed to originate from bone and affect its typical kidney and parathyroid targets, but in recent years, a growing number of studies had confirmed that it also acted on myocardial cells [16]. Patients with sepsis can keep their heart index normal or elevated by adequate volume resuscitation or by significantly reducing systemic vascular resistance with drugs. However, although the measured cardiac output increased and the stroke volume was normal, the myocardial dysfunction in patients with septic shock was still significant [17]. Importantly, 70%–90% of the mortality of patients with sepsis is significantly related to cardiovascular dysfunction, while the mortality of patients with sepsis without cardiovascular damage is about 20% [18]. Inflammation may affect cardiac compliance and function during the course of disease [19].

Secondly, we also found that FGF23 was consistent with biomarkers related to myocardial injury, such as TNI and BNP. From the experimental study, it can be seen that long-term high level of FGF23 can induce pathological left ventricular hypertrophy [20]. It is noteworthy that some studies had pointed out that the acutely elevated FGF23 had a positive inotropic effect in myocardial cells. In vitro study, it was found that FGF23 can cause cardiac hypertrophy by increasing the calcium influx and contractility of cardiac cells, verapamil, a calcium channel blocker, can eliminate this effect, FGF23 also increased ventricular muscle strip contractility (67%), which was inhibited by FGF receptor antagonism [21]. Recent studies had shown that FGF23 levels significantly increase during heart failure and were associated with cardiac complications and mortality [22]. The production of FGF23 was also found in fibroblasts after myocardial infarction. At the early stage of inflammation, the production of FGF23 was also detected through IL-6, IL-1β and TNF-α Stimulate cardiac fibroblasts to produce FGF23, while TGF (Transforming growth factor) -β inhibits the expression of FGF23 in the late stage of inflammation [23]. Therefore, FGF23 is regulated bilaterally in inflammatory state, which is consistent with our results. Presumably, this finding speculates the potential physiological role of elevated FGF23 in acute myocardial cell stress. Although a few studies had begun to explore the potential relationship between FGF23 and myocardial cells, it is still worth further exploration [24].

Studies had confirmed that long-term low level of klotho was an independent risk factor for cardiovascular and all-cause mortality in chronic hemodialysis patients and elderly people [25]. Emerging evidence demonstrated an anti-inflammatory action of klotho under pathological conditions [26], klotho overexpression significantly decreased IL-6 secretion. Animal experiments show that soluble klotho had a direct protective effect on cardiovascular system [27]. Existing evidence shows that klotho protein had antioxidant and anti-apoptotic activities, which can inhibit insulin/insulin-like growth factor-1 and TGF-β1, the signal pathway inhibited the release of pro-inflammatory cytokine IL-6 to fight inflammation and fibrosis [28]. And it was confirmed that klotho regulated TGF-β1-miR-132 axis can prevent cardiac remodeling and dysfunction induced by Ang II [28]. Unfortunately, we did not find a similar conclusion in the patients with septic shock. It was only observed that it may play a special role in myocardial injury, either as an "intermediary" or as a "participant".

Interestingly, our data on FGF23 was inconsistent with the clinical data published by previous researchers, but some commentators also questioned the previous data [29,30], which may be related to the different population and outcome time nodes.

5. Conclusion

In conclusion, in patients with septic shock and myocardial injury, the exacerbation of inflammation in the septic process was accompanied by a abnormal increase of circulating FGF23 level. FGF23 also subsided after the improvement of inflammation, and the opposite was true for patients who did not survive. The up-regulation of FGF23 may be involved in the response of patients to sepsis, and it is also speculated that FGF23 is involved in the myocardial injury of sepsis.

Ethics statement

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of Hangzhou Red Cross Hospital (No. 2021-245) and was performed in accordance with the Declaration of Helsinki. The patients/participants provided their written informed consent to participate in this study.

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Data availability statement

The data involved was all in the manuscript, and more detailed data content can be requested from the corresponding author.

Additional information

No additional information is available for this paper.

CRediT authorship contribution statement

Zheng Yang: Writing – review & editing, Writing – original draft, Methodology, Data curation, Conceptualization. **Jie Wang:** Writing – original draft, Methodology, Investigation. **Jilin Ma:** Writing – review & editing, Validation. **Danhong Ren:** Writing – review & editing, Conceptualization. **Zhihui Li:** Writing – review & editing, Conceptualization. **Kun Fang:** Writing – review & editing, Resources, Conceptualization. **Zhanli Shi:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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