The association between serum selenium concentration and prognosis in patients with heart failure in a Chinese population

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Whether Selenium (Se) deficiency relates with adverse prognosis in Chinese patients with heart failure (HF) is still unknown. This study aimed to investigate the association of serum Se level and the outcomes of patients with HF in a Chinese population. Patients with HF and serum Se examination were retrospectively included. Baseline information were collected at patient's first admission. The primary and secondary outcomes were all-cause mortality and rehospitalization for HF during follow-up, respectively. The study participants were divided into quartiles according to their serum Se concentrations. The Cox proportional hazard models were adopted to estimate the association of serum Se levels with observed outcomes. A total of 411 patients with HF with a mean age of 62.5 years were included. The mean serum level of Se was 68.3 ± 27.7 µg/L. There was nonsignificant difference of baseline characterizes between the four quartile groups. In comparison with patients in the highest quartile, those with the lowest quartile (17.40–44.35 µg/L) were associated with increased risk of all-cause mortality (adjusted hazard ratios (95% CI) 2.32 (1.43–3.77); P_trend = 0.001). Our study suggested that a lower serum Se level was significantly associated with increased risk of all-cause mortality in patients with HF.

Heart failure (HF) is an important disease burden worldwide with a 1–2% prevalence among global population1. Despite numerous advances in therapeutics of HF, there are still unmet needs to improve quality of life and long-term survival of those patients2. Patients with HF, especially for elderly, are commonly presented with malnutrition and micronutrients deficiency as underdetermined reasons3,4. Over last decade, several studies have found the associations between some trace elements deficiency (e.g. Zn, Fe) and adverse clinical outcomes in patients with HF5,6. Moreover, iron supplement has been evidenced to benefit HF patients with iron deprivation regarding to symptoms and exercise capacity7,8.

Selenium (Se) is an essential trace element for human health. Selenocysteine, the active form of Se, is incorporated as 25 selenoproteins including glutathione peroxidase (GPx), thioredoxin reductase, selenoprotein-P, redox-regulating signaling, and thyroid hormones metabolism3. The soil content of selenium is varying greatly, which can affect dietary selenium intake. For example, Venezuela, Canada, the United States and Japan have high intakes of Se (> 100 µg/day)9. In contrast, China has areas both with selenium deficiency and excess.

Severe Se deficiency has been proofed as a cause of congestive HF, a disorder known as Keshan Disease10, and less severe Se deficiency or suboptimal Se status has also been suggested associated with HF progression11. Recently, Bomer et al. using an European cohort of 2516 patients with HF reported that approximately 25% of patients with worsening HF have a serum Se < 70 µg/L, and that was associated with a poor quality of life and poor exercise capacity, as well as a worse prognosis12. However, serum Se levels vary greatly within different populations. In some regions such as China, Se deficiency maybe more common because of the Se-deficient soil and diet13,14. The prevalence of Se deficiency and whether it relates with adverse prognosis in Chinese patients with HF were still unknown.

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Therefore, this study aimed to investigate the association of serum Se level and the outcomes of patients with HF in a Chinese population.

Results

Patient selection and baseline characteristics. Between January 2015 and December 2018, 635 patients with confirmed HF were initially screened. Among them, 113 patients were excluded due to the absence of serum Se measurement. Sixty-seven patients were further excluded by thyroid disease (n = 42), treatment with amiodarone or glucocorticoids (n = 54), and severe systemic disease (n = 25). A total of 411 patients with HF with a mean age of 62.5 years were finally included (Table 1). The patients were less often female (44.5%), and had a markedly elevated level of N-terminal pro-B type natriuretic peptide (NT-proBNP) (3541 [IQR 1952–6909] pg/mL).

| Variables                      | Total   | 1st quartile (17.4–44.35 µg/L) (n = 104) | 2nd quartile (44.35–68.05 µg/L) (n = 102) | 3rd quartile (68.05–94.15 µg/L) (n = 103) | 4th quartile (94.15–116.7 µg/L) (n = 102) | P       |
|-------------------------------|---------|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|---------|
| Age (years)                   | 62.5 ± 15.9 | 60.0 ± 17.0                        | 62.1 ± 16.5                      | 63.8 ± 15.8                      | 64.0 ± 14.0                       | 0.223   |
| Female                        | 183 (44.5%)| 45 (43.3%)                         | 48 (47.1%)                       | 47 (45.6%)                       | 43 (42.2%)                        | 0.893   |
| BMI (kg/m²)                   | 26.7 ± 4.7 | 27.6 ± 4.6                         | 26.4 ± 4.5                       | 25.8 ± 4.8                       | 26.9 ± 4.7                        | 0.596   |
| Current smoker                | 82 (20.0%) | 18 (17.3%)                         | 19 (18.6%)                       | 16 (15.5%)                       | 29 (28.4%)                        | 0.093   |
| Current drinker               | 61 (14.8%) | 15 (14.4%)                         | 17 (16.8%)                       | 9 (8.7%)                         | 20 (19.6%)                        | 0.562   |
| BMI (kg/m²)                   | 26.7 ± 4.7 | 27.6 ± 4.6                         | 26.4 ± 4.5                       | 25.8 ± 4.8                       | 26.9 ± 4.7                        | 0.596   |

Table 1. Baseline characteristics of the study population stratified by quartile of serum Se concentration. Data are presented as mean (standard deviation), median (interquartile range), or n (%). BMI body mass index, NT-proBNP n-terminal pro brain natriuretic peptide, CKD chronic kidney disease, AF atrial fibrillation, IVST interventricular septum thickness, PWT posterior wall thickness, LVDv left ventricular end-diastolic volume, LVSw left ventricular end-systolic volume, LVEF left ventricular ejection fraction, LAD left atrial dimension, CCB calcium-channel blocker, ARB angiotensin receptor blocker, ACE-I angiotensin converting enzyme inhibitor.
The 80% of patients were in New York Heart Association (NYHA) function class III-IV. A majority of patients (71.8%) were identified as having a prior history of HF, the mean duration of HF was 20 ± 14 months. Nearly one-fourth of patients presented with acute or worsening decompensated HF at admission. According to left ventricle ejection fraction (EF), the prevalence was 47.2% of HF with preserved EF (n = 194), as well 20.4% (n = 84) of HF with mid-range EF and 32.4% (n = 132) of HF with reduced EF.

Among medical history, coronary artery disease (45%) was the most common ischemic etiology, followed by dilated cardiomyopathy (14%). Hypertension and diabetes mellitus were identified in 40.9% and 27.3% of patients, respectively. Moreover, 29.4% of patients had concomitant atrial fibrillation. The mean serum level of Se of all included patients with HF was 68.3 ± 27.7 µg/L. When patients were categorized by quartiles of serum concentration, there was nonsignificant difference between the four groups (Table 1).

Comparison between survival and deceased patients. During a median of 23 (15–37) months follow-up, 131 (31.9%) death and 216 (52.6%) rehospitalization for HF were observed. Compared to survival patients with HF, those deceased patients had a reduced serum Se concentration (72.4 ± 25.9 µg/L vs. 59.4 ± 29.4 µg/L; P < 0.001) (Table 2). Moreover, those patients were more often older, and more likely to have higher body mass index (BMI) value, higher NT-proBNP level, and larger left atrial diameter. Chronic kidney disease was also

| Variables | Survival patients (n = 280) | Deceased patients (n = 131) | P |
|-----------|---------------------------|----------------------------|---|
| Age (years) | 61.2 ± 16.0 | 65.1 ± 15.4 | 0.022 |
| Female | 118 (42.1%) | 65 (49.6%) | 0.167 |
| BMI (kg/m²) | 26.1 ± 4.6 | 27.9 ± 4.6 | <0.001 |
| Current smoker | 58 (20.7%) | 24 (18.3%) | 0.599 |
| Current drinker | 42 (15.1%) | 19 (14.5%) | 1.000 |

Table 2. Comparison of survival and deceased patients with heart failure. Data are presented as mean (standard deviation), median (interquartile range), or n (%). Abbreviation as in Table 1.
more frequently in patients who died, while statin and angiotensin converting enzyme inhibitor were less prescribed to them.

**Serum Se concentration and all-cause mortality.** There were 26 (25.5%) all-cause mortality events occurred in patients with HF in the 1st quartile serum Se concentration, 26 (25.2%) events in the 2nd quartile, 27 (26.5%) events in the 3rd quartile, and 52 (50.0%) events in the 4th quartile, respectively. The Kaplan–Meier survival examination showed the poorest prognosis in patients with HF with the lowest serum Se concentration (log-rank $P=0.005$) when compared with the remained three groups (Fig. 1). In comparison with patients in the highest quartile, those with the lowest quartile (17.4–44.35 µg/L) were associated with increased risk of all-cause mortality [adjusted hazards ratios (95% CI) 2.32 (1.43–3.77); $P_{\text{trend}}=0.001$] (Table 3; Fig. 2). In subgroup analy-
ses, the similar effect directions with the main results were observed in each subgroup although the magnitudes were attenuated (Tables 4, 5). And nonsignificant interactions existed in different subgroups.

Serum Se concentration and rehospitalization. There were 57 (55.9%) rehospitalization for HF events occurred in patients with HF in the 1st quartile serum Se concentration, 50 (48.5%) events in the 2nd quartile, 43 (42.2%) events in the 3rd quartile, and 66 (63.5%) events in the 4th quartile. The Kaplan–Meier survival curve revealed the similar incidences of rehospitalization within the four groups patients with HF, even though the difference was significant (log-rank P = 0.026) (Fig. 1). The COX survival models failed to find a positive association between serum Se concentration with rehospitalization event in patients with HF. Subgroup analyses demonstrated the similar findings with the main results across different subgroups.

Table 3. The associations of serum selenium with prognosis in patients with heart failure. Data are completed for all variables. Model 1: no adjustment; Model 2: adjusted for age, sex, body mass index, smoking, drinking, hypertension, diabetes, chronic kidney disease, prior history of heart failure, and atrial fibrillation; Model 3: further adjusted for medication.

|                  | Model 1       | Model 2       | Model 3       |
|------------------|---------------|---------------|---------------|
|                  | HR (95% CI)   | P             | HR (95% CI)   | P             | HR (95% CI)   | P             |
| **Rehospitalization** |               |               |               |               |               |               |
| 4th quartile (94.15–116.7 μg/L) | Ref           | Ref           | Ref           |               |               |               |
| 3rd quartile (68.05–94.15 μg/L) | 0.92 (0.63–1.34) | 0.648         | 0.99 (0.67–1.46) | 0.940       | 0.99 (0.67–1.47) | 0.953       |
| 2nd quartile (44.35–68.05 μg/L) | 0.72 (0.48–1.07) | 0.103         | 0.77 (0.51–1.15) | 0.201       | 0.76 (0.51–1.15) | 0.764       |
| 1st quartile (17.4–44.35 μg/L) | 1.34 (0.94–1.92) | 0.105         | 1.30 (0.90–1.88) | 0.160       | 1.31 (0.90–1.89) | 0.155       |
| Trend test       |               |               |               |               |               |               |
|                   | 0.247         |               | 0.330         |               | 0.324         |               |
| Every 5 μg/L decrease | 1.08 (0.96–1.01) | 0.132       | 1.02 (0.99–1.04) | 0.182       | 1.02 (0.99–1.04) | 0.185       |
| **All-cause mortality** |               |               |               |               |               |               |
| 4th quartile (94.15–116.7 μg/L) | Ref           | Ref           | Ref           |               |               |               |
| 3rd quartile (68.05–94.15 μg/L) | 1.00 (0.58–1.72) | 0.990       | 1.15 (0.66–2.00) | 0.628       | 1.12 (0.64–1.96) | 0.681       |
| 2nd quartile (44.35–68.05 μg/L) | 1.02 (0.59–1.75) | 0.948       | 1.06 (0.62–1.84) | 0.824       | 1.06 (0.61–1.84) | 0.831       |
| 1st quartile (17.4–44.35 μg/L) | 2.40 (1.50–3.85) | < 0.001     | 2.34 (1.44–3.80) | 0.001       | 2.32 (1.43–3.77) | 0.001       |
| Trend test       |               |               |               |               |               |               |
|                   | < 0.001       |               | 0.001         |               | 0.001         |               |
| Every 5 μg/L decrease | 1.08 (1.04–1.12) | < 0.001     | 1.07 (1.04–1.11) | < 0.001     | 1.07 (1.04–1.11) | < 0.001     |

Figure 2. Shapes of the concentration–response relationships of serum selenium and risk of mortality.
To date, we firstly investigated the relationship between serum Se concentration and prognosis in Chinese patients with HF. Our findings suggest that serum Se concentration was decreased in those patients died during follow-up, and the lower serum Se level was significantly associated with all-cause mortality in patients with HF. However, similar association was not identified between this marker and rehospitalization for HF in these patients.

The Se intake in human body has been known to largely depend on the level of Se in soil, thus leading to a variety of serum Se concentration among different population. The Se deficiency was the well-defined cause of an endemic cardiomyopathy called Keshan disease in China, which was characterized as congestive HF and sequent high case-fatality rate. With the increased knowledge in metabolism of trace elements, the role of Se has been related to morbidity and mortality in several diseases. In a Germany study included 1731 individuals with coronary artery disease, low Se concentration was found to be associated with future cardiovascular death in patients with acute coronary syndrome during a median follow-up of 6.1 years. Lee et al. had reported that low serum selenium levels in patients with respiratory diseases have a significant relationship with poor prognosis.

**Table 4.** Subgroup analyses for associations between serum selenium and the risk of mortality in patients with heart failure. Adjusted for age, sex (except in the sex-stratified analysis), body mass index, smoking (except in the smoking-stratified analysis), drinking (except in the alcohol-stratified analysis), hypertension, diabetes, chronic kidney disease, prior history of heart failure, atrial fibrillation and medication.

| Covariates    | Death/participants | HR (95% CI)  | P  |
|---------------|--------------------|--------------|----|
| Sex           |                    |              |    |
| Male          | 66/228             | 1.07 (1.02–1.12) | 0.007 |
| Female        | 65/183             | 1.07 (1.02–1.13) | 0.004 |
| Age (years)   |                    |              |    |
| <75           | 95/309             | 1.06 (1.02–1.10) | 0.002 |
| ≥75           | 36/102             | 1.11 (1.03–1.20) | 0.009 |
| BMI (kg/m²)   |                    |              |    |
| <25           | 46/170             | 1.02 (0.96–1.08) | 0.581 |
| ≥25           | 85/241             | 1.09 (1.05–1.14) | <0.001 |
| Smoking status|                    |              |    |
| Never         | 107/329            | 1.06 (1.02–1.15) | 0.001 |
| Ever          | 24/82              | 1.13 (1.03–1.25) | 0.011 |
| Alcohol drinking|                |              |    |
| Seldom        | 112/350            | 1.06 (1.02–1.10) | <0.001 |
| Occasional or regular | 19/61   | 1.15 (1.03–1.29) | 0.016 |

**Table 5.** Subgroup analyses for associations between serum selenium and the risk of rehospitalization in patients with heart failure. * Adjusted for age, sex (except in the sex-stratified analysis), body mass index, smoking (except in the smoking-stratified analysis), drinking (except in the alcohol-stratified analysis), hypertension, diabetes, chronic kidney disease, prior history of heart failure, atrial fibrillation and medication.

| Covariates    | Rehospitalization/participants | HR (95% CI)  | P* |
|---------------|--------------------------------|--------------|----|
| Sex           |                                |              |    |
| Male          | 66/228                         | 1.03 (1.00–1.07) | 0.097 |
| Female        | 65/183                         | 1.00 (0.97–1.04) | 0.882 |
| Age (years)   |                                |              |    |
| <75           | 95/309                         | 1.01 (0.97–1.04) | 0.369 |
| ≥75           | 36/102                         | 1.03 (0.98–1.08) | 0.276 |
| BMI (kg/m²)   |                                |              |    |
| <25           | 46/170                         | 0.96 (0.92–1.01) | 0.090 |
| ≥25           | 85/241                         | 1.04 (1.01–1.08) | 0.009 |
| Smoking status|                                |              |    |
| No            | 107/329                        | 1.01 (0.98–1.04) | 0.704 |
| Yes           | 24/82                          | 1.06 (1.00–1.12) | 0.061 |
| Alcohol drinking|                              |              |    |
| No            | 112/350                        | 1.01 (0.98–1.04) | 0.598 |
| Yes           | 19/61                          | 1.08 (0.99–1.16) | 0.071 |

**Discussion**

To date, we firstly investigated the relationship between serum Se concentration and prognosis in Chinese patients with HF. Our findings suggest that serum Se concentration was decreased in those patients died during follow-up, and the lower serum Se level was significantly associated with all-cause mortality in patients with HF. However, similar association was not identified between this marker and rehospitalization for HF in these patients.

The Se intake in human body has been known to largely depend on the level of Se in soil, thus leading to a variety of serum Se concentration among different population. The Se deficiency was the well-defined cause of an endemic cardiomyopathy called Keshan disease in China, which was characterized as congestive HF and sequent high case-fatality rate. With the increased knowledge in metabolism of trace elements, the role of Se has been related to morbidity and mortality in several diseases. In a Germany study included 1731 individuals with coronary artery disease, low Se concentration was found to be associated with future cardiovascular death in patients with acute coronary syndrome during a median follow-up of 6.1 years. Lee et al. had reported that low serum selenium levels in patients with respiratory diseases have a significant relationship with poor prognosis on
admission\textsuperscript{16}. However, the randomized controlled trials with Se supplements failed to find preventive effect of Se on the incidence of type 2 diabetes, cancers, and thyroid disease\textsuperscript{17–19}. These results have caused more confusions about the real physiological role of Se. Despite all this, there are still raising interests upon the potential association between serum Se level and the outcomes of HF\textsuperscript{20}. The important consideration is the possible benefit from Se homeostasis maintenance to improve the high prevalence of malnutrition and poor prognosis in patients with HF\textsuperscript{21}. Although the decreased Se level was frequent in patients with HF compared to health controls\textsuperscript{12,22,23}, the definitely correlation between this reduction and long-term survival was not well-established. Recently, an European multinational prospective cohort study revealed a 20.4\% of Se deficiency among 2516 worsening HF patients, and found this deficiency in HF patients is independently associated with impaired exercise tolerance and a 50% higher mortality rate\textsuperscript{12}. In the current study, we also observed a high prevalence of Se deprivation in Chinese patients with HF in the setting of previously reported reference of 70 μg/L\textsuperscript{13}. Furthermore, our results showed the trend of inverse association between serum Se level significantly and all-cause mortality in patients with HF, which was in line with prior study’s findings. As a result, these aforementioned results have made the foundation for the further randomized controlled trials to assess the feasibility, safety and effectiveness of Se supplements in patients with HF.

The underlying mechanisms of Se in the onset and progression of HF are multifactorial. The Se plays a vital role in the function of the antioxidant GPx enzymes, the main intracellular antioxidant. The GPx enzymes could remove hydrogen peroxide and the harmful lipid hydroperoxides generated in vivo by oxygen-derived species, which are very important defense mechanisms in humans\textsuperscript{24}. Another important selenoprotein, called Selenoprotein P, has been identified to be a major extracellular antioxidant, and involved in acute HF\textsuperscript{25}. Se is also known to affect thyroid hormone metabolism and the synthesis and activity of deiodinases, enzymes converting thyroxin into the biologically active triiodothyronine\textsuperscript{26}. In animal experiments, Se deficiency led to reactive myocardial fibrosis and systolic dysfunction accompanied by increased myocardial oxidant stress via effects on Redox–Methylation balance\textsuperscript{27}. Furthermore, Se supplementation lowers insulin resistance and markers of cardiometabolic risk in patients with congestive HF, which might inform the potential benefits of Se supplements\textsuperscript{28}.

There are some limitations need interpreting. First, this study was limited by retrospective design, and the sample size might be unable to reach statistical power especially in subgroup analyses. Second, we could not identify a “true” Se deficiency status because of the missing of reference ranges for serum Se level in China. As such, reference ranges from European countries might not be suggested to apply in Chinese population considering China was classified as low Se region. Third, even though a number of confounders were adjusted, we cannot rule out the possibility that unmeasured factors or residual confounders might contribute to the associations our study observed. Finally, the observational data analysis of the associations between markers of Se status and prognosis in patients with HF make it impossible for us to investigate the causal conclusion. However, the prospective association from European cohort also suggests that lower serum Se levels were positively associated with long-term prognosis in patients with HF.

In conclusion, serum low Se concentration was common in Chinese patients with HF. The lower serum Se level was significantly associated with increased risk of all-cause mortality in these patients.

Methods

**Patients.** Consecutive patients with acute or chronic HF aged 18 years or older were consecutively included for initial screening. All patients were from the Nanyang Central Hospital, Nanyang, Henan, China, where was defined as adequate- and low-selenium area. The electronic medical records were retrospectively reviewed and the diagnosis of HF was based on typical clinical manifestations and signs, such as breathlessness, paroxysmal nocturnal dyspnea, reduced exercise tolerance, jugular vein distension or peripheral edema, plasma NT-proBNP and echocardiography findings according to the current guideline\textsuperscript{29}. A cutoff value of 125 pg/mL or 300 pg/mL for NT-proBNP was used in the diagnostic algorithm of acute HF and chronic HF, respectively. The patients with serum Se examination would be finally included after the following exclusion criteria were all satisfied: thyroid disease, treatment with amiodarone or glucocorticoids, and severe systemic disease such as infectious, inflammatory, autoimmun, or neoplastic disease. At admission, patients with HF received the standard treatments that guideline recommended, whereas the etiological treatments were dependent on patient's condition and at physician's discretion. The study protocol was in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Nanyang Central Hospital. The informed consent was obtained from all participants before participating the study.

**Data collection.** Information on demography, laboratory tests, co-morbidities, echocardiography examinations and medication treatments were collected at patient's first admission. After admission to hospital, five milliliter blood sample was withdrawn from each participants after a 12 h fasting period. Serum was immediately separated from whole blood and stored at ~ 80 °C until analysis. The carbon-furnace atomic-absorption spectrometry and Zeeman compensation was used to determine the serum Se concentrations by a Spectra AA 220 Z (Varian). NT-proBNP levels were measured using electrochemiluminescent immunoassay (ECLIA) method by a VIDAS 30 (bioMerieux). The transthoracic echocardiographic evaluation was performed during hospitalization and records were reviewed by a senior echocardiographer.

**Outcomes and follow-up.** The primary outcome of interest in this study was all-cause mortality. The secondary outcome was rehospitalization for HF. All patients were followed up via clinic visit, phone or internet interview, until death or rehospitalization event occurred, or up to June 2020 or the last follow-up if index event did not occur. The survival data was censored at the end of the follow-up time.
Statistical methods. The numerical variables are presented as mean (standard deviations [SD]) or median (interquartile range [IQR]) according to distribution patterns. The categorical variables are presented as count with frequencies. One-way analysis of variance, the Kruskal–Wallis test, the Student’s t test and the Pearson’s chi-square test were applied, as indicated, for comparisons of between-group difference. The study participants were divided into quartiles according to their serum Se concentrations. Kaplan–Meier survival curves were constructed and the log-rank test was used to compare either death or rehospitalizations as events in different groups. The Cox proportional hazard models were adopted to estimate the association of serum Se levels with the primary outcome and secondary outcome. Three models were adopted: Model 1, without any adjustment; Model 2, adjusting for age, sex, BMI, NT-proBNP, smoking, drinking, hypertension, diabetes, chronic kidney disease, prior history of HF, and atrial fibrillation; Model 3, further adjusting for medication treatment. The concentration–response curve was then evaluated using a natural cubic spline.

Subgroup analyses were also conducted to investigate whether the associations were modified by sex (male or female), age (< 75 or ≥ 75 years), BMI (< 25 or ≥ 25 kg/m²), smoking status (never or ever), and drinking (yes or no). Each potential modifier was examined in a separate model by adding a multiplicative interaction term (i.e., potential modifier * Se concentration).

All statistical analyses were conducted using SPSS 21.0 for Windows (SPSS, Inc., Chicago, USA), and two-sided P < 0.05 was considered statistically significant.

Ethical approval. The study protocol was in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Nanyang Central Hospital. The informed consent was obtained from all participants before participating the study.

Data availability Additional data are available from the corresponding author for reasonable requesting.

References

1. Mosterd, A. & Hoes, A. W. Clinical epidemiology of heart failure. Heart (Brit. Cardiac. Soc.) 93, 1137–1146. https://doi.org/10.1136/hrt.2003.025270 (2007).
2. Dokainish, H. et al. Global mortality variations in patients with heart failure: Results from the International Congestive Heart Failure (INTER-CHF) prospective cohort study. Lancet Glob. Health 5, e665–e672. https://doi.org/10.1016/s2214-109x(17)30196-1 (2017).
3. Jacobsson, A., Pihl-Lindgren, E. & Fridlund, B. Malnutrition in patients suffering from chronic heart failure; the nurse’s care. Eur. J. Heart Fail. 3, 449–456. https://doi.org/10.1016/S1388-9842(01)00139-8 (2001).
4. Cvetinovic, N. et al. Micronutrient depletion in heart failure: Commonly, clinically relevant and treatable. Int. J. Mol. Sci. https://doi.org/10.3390/ijms2025267 (2019).
5. Alexanian, I. et al. Clinical and echocardiographic correlates of serum copper and zinc in acute and chronic heart failure. Clin. Res. Cardiol. 103, 938–949. https://doi.org/10.1007/s00392-014-0735-x (2014).
6. Jankowska, E. A. et al. Iron deficiency: An ominous sign in patients with systolic chronic heart failure. Eur. Heart J. 31, 1872–1880. https://doi.org/10.1093/eurheartj/ehq158 (2010).
7. Anker, S. D. et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. N. Engl. J. Med. 361, 2436–2448. https://doi.org/10.1056/NEJMoa0908355 (2009).
8. Ponikowski, P. et al. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. Eur. J. Heart J. 36, 657–668. https://doi.org/10.1002/ehj.21835 (2015).
9. Reeves, M. A. & Hofmann, P. R. The human selenoproteome: Recent insights into functions and regulation. Cell. Mol. Life Sci. 66, 2457–2478. https://doi.org/10.1007/s00018-009-0032-4 (2009).
10. Rayman, M. P. Selenium and human health. Lancet (Lond., Engl.) 379, 1256–1268. https://doi.org/10.1016/s0140-6736(11)61452-9 (2012).
11. Ge, K. & Yang, G. The epidemiology of selenium deficiency in the etiological study of endemic diseases in China. Am. J. Clin. Nutr. 57, 259s–263s. https://doi.org/10.1093/ajcn/57.2.259s (1993).
12. Ghaemian, A., Salehifar, E., Shiraj, H. & Babaee, Z. A comparison of selenium concentrations between congestive heart failure patients and healthy volunteers. J. Tehran Heart Center 7, 53–57 (2012).
13. Bomer, N. et al. Selenium and outcome in heart failure. Eur. J. Heart Fail. https://doi.org/10.1002/ejhf.1644 (2019).
14. Alissa, E. M., Bahjiri, S. M. & Ferna, G. A. The controversy surrounding selenium and cardiovascular disease: A review of the evidence. Med. Sci. Monit. Int. Med. J. Exp. Clin. Res. 9, 9–18 (2003).
15. Lodis, E. et al. Serum selenium and prognosis in cardiovascular disease: Results from the Atheroscreen study. Atherosclerosis 209, 271–277. https://doi.org/10.1016/j.atherosclerosis.2009.09.008 (2010).
16. Lee, Y. H. et al. Serum selenium levels in patients with respiratory diseases: A prospective observational study. J. Thorac. Dis. 8, 2068–2078. https://doi.org/10.21037/jtd.2016.07.60 (2016).
17. Stranges, S. et al. Effects of long-term selenium supplementation on the incidence of type 2 diabetes: A randomized trial. Ann. Intern. Med. 147, 217–223. https://doi.org/10.7326/m13-4819-147-4-20070821-00175 (2007).
18. Lippman, S. M. et al. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: The Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA 301, 39–51. https://doi.org/10.1001/jama.2008.864 (2009).
19. Kahaly, G. J., Riedl, M., König, J., Diana, T. & Schomburg, L. Double-blind, placebo-controlled, randomized trial of selenium in Graves hyperthyroidism, J. Clin. Endocrinol. Metab. 102, 4333–4341. https://doi.org/10.1210/jc.2017-01736 (2017).
20. McKeag, N. A., McKinley, M. C., Woodside, J. V., Harbinson, M. T. & McKeown, P. P. The role of micronutrients in heart failure. J. Acad. Nutr. Diet. 112, 870–886. https://doi.org/10.1016/j.jand.2012.01.016 (2012).
21. Nicol, S. M., Carroll, D. L., Homeyer, C. M. & Zamagni, C. M. The identification of malnutrition in heart failure patients. Eur. J. Cardiovasc. Nurs. 1, 139–147. https://doi.org/10.1177/1474-51190200005-1 (2002).
22. Fączek-Jucha, M. et al. Selenium deficiency and the dynamics of changes of thyroid profile in patients with myocardial infarction and chronic heart failure. Kardiol. Pol. 77, 674–682. https://doi.org/10.33963/kp.14822 (2019).
23. Mirdamadi, A., Rafiei, R., Kahazaipour, G. & Fouladi, L. Selenium level in patients with heart failure versus normal individuals. Int. J. Prev. Med. 10, 210. https://doi.org/10.4103/ijpvm.IJPVM_45_18 (2019).
24. de Lorgeril, M. & Salen, P. Selenium and antioxidant defenses as major mediators in the development of chronic heart failure. *Heart Fail. Rev.* **11**, 13–17. https://doi.org/10.1007/s10741-006-9188-2 (2006).

25. Jutila, A. et al. Selenoprotein P deficiency and risk of mortality and rehospitalization in acute heart failure. *J. Am. Coll. Cardiol.* **74**, 1009–1011. https://doi.org/10.1016/j.jacc.2019.06.023 (2019).

26. Köhrle, J., Jakob, F., Contempré, B. & Dumont, J. E. Selenium, the thyroid, and the endocrine system. *Endocr. Rev.* **26**, 944–984. https://doi.org/10.1210/er.2001-0034 (2005).

27. Metes-Kostik, N. et al. Both selenium deficiency and modest selenium supplementation lead to myocardial fibrosis in mice via effects on redox-methylation balance. *Mol. Nutr. Food Res.* **56**, 1812–1824. https://doi.org/10.1002/mnfr.201200386 (2012).

28. Raygan, F. et al. Selenium supplementation lowers insulin resistance and markers of cardio-metabolic risk in patients with congestive heart failure: A randomised, double-blind, placebo-controlled trial. *Br. J. Nutr.* **120**, 33–40. https://doi.org/10.1017/s0007114518001253 (2018).

29. Ponikowski, P. et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur. Heart J.* **37**, 2129–2200. https://doi.org/10.1093/eurheartj/ehw128 (2016).

**Author contributions**
C.G.Q. conceived and designed research. Z.L.Z., C.C., Y.X.Z., and Z.Y.C. collected data. Z.L.Z. and J.B.L. performed data analysis. Z.L.Z. drafted the manuscript. All authors revised the manuscript and approved the final version.

**Competing interests**
The authors declare no competing interests.

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