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High exposure to heavy metals such as cadmium, lead, arsenic and mercury can cause nephrotoxicity.

A study highlights the protective effects of micronutrients against chronic kidney disease (CKD). While high blood levels of heavy metals increased the risk of CKD, elevated plasma selenium and serum zinc levels may interact with low-toxicity heavy metals to reduce CKD risk.

Illustration by Ngiam Li Yi

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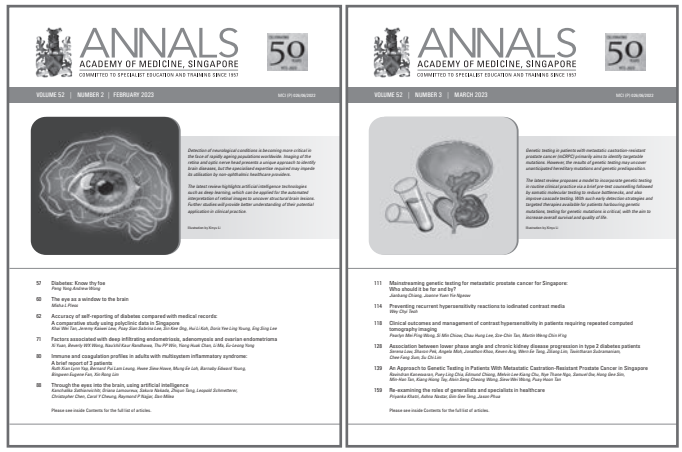

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EDITORIALS

ORIGINAL ARTICLES

LETTERS TO THE EDITOR

EDITORIAL

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Micronutrients and kidney health

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Chronic kidney disease (CKD) is a structural and functional disorder of the kidney caused by many diseases, such as diabetes, hypertension and glomerular disease.[1] There are many factors that contribute to the development and progression of CKD, and often, we do not look at the exposure of heavy metals as a risk factor for the development and accelerant of CKD.[2] Heavy metals, such as cadmium, mercury, arsenic and lead, can enter the body through various sources, including contaminated water, food, air pollution, occupational exposure and certain medications. Prolonged or excessive exposure to these metals can lead to their accumulation in the kidneys and cause nephrotoxicity. The kidney has the ability to reabsorb and concentrate divalent ions and metals. The renal proximal tubules are responsible for the reabsorption of essential substances from the glomerular filtrate. Heavy metals in the blood can bind to metallothionein and glutathione in inert forms, and the conjugates are then released into the blood through the liver and kidneys. These substances are then reabsorbed through the endocytic process in the S1 segment of the proximal tubule, which may eventually lead to chronic inflammation, renal fibrosis and renal failure.

Trace elements and vitamins, collectively known as micronutrients, are essential for maintaining normal human physiology.[3-5] Adequate intake of these micronutrients is vital for the proper functioning of various biological processes, including metabolism, immune function, antioxidant defence and enzymatic reactions. Selenium and zinc are essential micronutrients for maintaining human health. Selenium contributes to the regulation of gastrointestinal function, improvement of human immunity, antioxidant activity and cell repair. Zinc is involved in regulating appetite, supporting a healthy immune system, wound healing, vitamin A absorption and enzymatic functions. In diabetic patients, zinc has several positive effects and CKD is associated with lower zinc concentrations.[3] Deficiency of micronutrients is associated with more rapid progression of CKD.[4] Lower blood selenium is associated with an increased incidence of CKD and increased mortality in haemodialysis-dependent CKD patients.[5,6] Zinc supplementation may protect the kidney by reducing blood glucose levels, microalbuminuria and alleviating glomerular damage.[3]

In this issue of the *Annals*, Lin et al. explored associations between CKD and heavy metal exposures measured in blood or urine among the community-dwelling population, and whether and how selenium and zinc modify the associations.[7] Data for this cross-sectional retrospective cohort study were extracted from the National Health and Nutrition Examination Survey (NHANES) database of the US Centers for Disease Control and Prevention's National Center for Health Statistics. Adults aged 18 years or older, who had complete information for the variables of interest, were included but subjects with end-stage renal disease (ESRD), defined as a glomerular filtration rate (GFR) of <15 mL/min/1.73 m^2, were excluded. The study population was divided into subjects with or without CKD, defined as having a GFR <60 mL/min/1.73 m^2 for further comparisons. Three types of associations were evaluated: (1) roughly linear associations between log10 GFR and blood lead, cadmium, mercury, urinary arsenic, plasma selenium, serum zinc, and serum and red blood cell (RBC) folate; (2) crude and adjusted associations between the presence of CKD and quartiles of blood metals, urinary arsenic, plasma selenium, serum zinc, and serum and RBC folate; (3) combined effects of blood metals, urinary arsenic, and plasma selenium or serum zinc on CKD. In this large population-based study, the authors found that micronutrients had a protective effect in CKD patients with high blood heavy metals. Individuals with elevated blood levels of toxic heavy metals had an increased likelihood of CKD, which decreased with higher plasma selenium and serum zinc concentrations. There appears to be interactions between high levels of zinc and toxic heavy metals that reduce the risk of CKD.

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These results suggest that increasing the levels of zinc and selenium in the body and avoiding exposure to heavy metals may prevent CKD.

While these findings are intriguing, the study is limited by its observational, cross-sectional, retrolective design and non-standard collection time points of urine and blood. Thus, the inferences of causality are also limited. The results may not be generalisable to other populations, and single measurements of nephrotoxic metals may not reflect cumulative exposure. More comprehensive, observational and interventional studies are needed to determine whether clinical supplementation with selenium and zinc reduces CKD risk in people exposed to heavy metals.

Current clinical practice does not fully evaluate the micronutrient status of pre-dialysis and dialysis-dependent CKD patients due to lack of data and intervention studies.[8] The most common causes of CKD and ESRD in Singapore are diabetes and hypertension, both of which are lifestyle-related and non-communicable non-communicable diseases.[1] The micronutrient status of diabetic CKD patients in Singapore and the general population is unclear. Further studies are needed to identify CKD patients with micronutrient deficiencies and perform trials to determine if supplementation for diagnosed CKD patients can improve clinical outcomes; or if fortifying food with zinc and selenium may protect the public at large from CKD. While selenium and zinc are essential for health, excessive intake can have adverse effects. It is generally recommended to obtain these micronutrients through a balanced diet or based on recommend daily allowances.[8] Supplementation should be considered under the guidance of a healthcare professional if deficiencies are identified, especially in CKD patients who are prescribed restrictive diets as part of the nutritional management of CKD.[9]

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EDITORIAL

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Impact of pre-existing depression on severe COVID-19 outcomes

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The outbreak of the COVID-19 virus in 2019 had rapidly developed into a global pandemic, causing more than 6.8 million deaths and impacting the lives of billions of individuals around the world.[1] Public healthcare around the work have mainly focused on the clinical manifestations and treatment of the deadly respiratory disease. As the pandemic progressed, it became clear that the psychological distress—arising from anxiety, depression and self-isolation; leading even to some suicides—had negatively impacted people's mental health.[2] However, whether pre-existing mental disorder has an influence on COVID-19 outcomes remains unknown.

There is evidence highlighting how patients with pre-existing depression might be vulnerable in the context of COVID-19 pandemic, not only because of their mental disorders, but also due to long-term effects of medication and comorbid physical health problems.[3] The combined factors mean that these patients are vulnerable to the virus as well as the negative effects of public health measures ranging from repeated lockdown, periods of self-isolation and disruption to normal healthcare. Specifically, it is unclear how the prevalence of depression may affect patients who contract COVID-19. This is compounded by the challenge in defining and providing evidence of pre-existing mental disorder in a large-scale cohort.

Against this background, authors Su Kyong Lee et al. in a recent *Annals* article conducted a study in South Korea to investigate the association between patients with pre-existing depressive conditions and severe COVID-19 events.[4] The population-based cohort covered 97% of all South Korean citizens, where 29,106 eligible patients were screened into the analytic cohort and 6,079 among them showed depressive symptoms. Patients with moderate-to-severe depressive symptoms were shown to be mostly of a younger age, women, of lower income, and who had no COVID-19 vaccination. The findings are consistent with global findings on mental health issues.[5] Furthermore, a study conducted across 204 countries[6] revealed a prevalence of 3152.9 cases for depressive symptoms and 4802.4 cases anxiety disorders per 100,000-population, respectively. The stress was mainly attributed to the worry of increasing infection rates and reductions in human mobility.

Findings by the authors showed that pre-existing depressive status (i.e. diagnosed before the pandemic) was associated with a higher risk of severe clinical COVID-19 events including requirement of various oxygen therapies, admission to ICU, extracorporeal membrane oxygenation (ECMO) and even death. Furthermore, moderate-to-severe depressive symptoms led to a significantly higher risk of severe COVID-19 events when compared to participants without depressive symptoms. These results did not change with vaccination status. The bidirectional association between mental health disorders and severe virus infection has been supported by several studies, where the vulnerability of the immune system and increased level of inflammatory cytokines induced by pre-existing depressive status are suggested as reasons facilitating the occurrence of severe COVID-19 events.[7] Additionally, mental disorder accompanied by obesity, low systolic pressure and diabetes before the pandemic makes individuals more susceptible to COVID-19 infection.[8] This analysis based on large population-level data provides the evidence supporting the association between pre-existing depression and increased risk of severe COVID-19.

The implications of severe COVID-19 events for people with pre-existing depression are of great concern. Against this context, mental health support is a priority for both patients and policymakers. Early intervention for patients with mental health disorders can reduce negative mental health problems and improve treatment effectiveness.[9] This requires timely mental health assessment to identify people with pre-existing depression, and extending to them sustained support and treatment from psychological services. In addition, pandemic-related lockdowns and restrictions in social contact require for new systems of healthcare. A rapid shift from conventional outpatient service to telemedicine or digital medicine has emerged in this global crisis.[10] This change has the potential to provide more

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accessible mental health platforms that enable patients seek psychological treatment via the internet without physical face-to-face consultations with doctors. Telemedicine may also sidestep the issue of stigma when seeking psychological advice and provide greater privacy for patients with mental health disorders to be treated from their homes. According to recent reports in the US, telemedicine has greatly improved the lives of patients suffering from depression and other mental health issues.[11] However, it is noted that no telemedicine programme can be created overnight, and clear rules and regulation by governments and health organisations are necessary for strong system integration and data privacy protection. Last but not least, seeing how patients with depression were impacted in the COVID-19 pandemic should remind us to watch out for this vulnerable group in the next crisis. Governments and healthcare workers can be more vigilant regarding the welfare of this group of individuals—with more dedicated care pathways and monitoring and support the patients—and hopefully assisted by greater awareness among the general population for those with multiple medical problems.

The COVID-19 pandemic presents not only a respiratory disease but also a public mental health challenge. As the authors described in the *Annals*, repeated episodes of lockdown, self-isolation and fear of unemployment have put more pressure on patients whose mental health were already affected before pandemic. The pre-existing mental disorders in turn caused higher risks of severe COVID-19 events and outcomes. Thus, it is crucial for countries to increase awareness of vulnerable groups as well as to provide timely public mental health interventions for individuals with depression. We must focus and integrate our public mental health support targeting groups at high risk of mental disorder in order to be ready for future crises.

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ORIGINAL ARTICLE

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Association of anticoagulation use during continuous kidney replacement therapy and 90-day outcomes: A multicentre study

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ABSTRACT

Introduction: Anticoagulation is recommended during continuous kidney replacement therapy (CKRT) to prolong the filter lifespan for optimal filter performance. We aimed to evaluate the effect of anticoagulation during CKRT on dialysis dependence and mortality within 90 days of intensive care unit (ICU) admission.

Method: Our retrospective observational study evaluated the first CKRT session in critically ill adults with acute kidney injury (AKI) in Singapore from April to September 2017. The primary outcome was a composite of dialysis dependence or death within 90 days of ICU admission; the main exposure variable was anticoagulation use (regional citrate anticoagulation [RCA] or systemic heparin). Multivariable logistic regression was performed to adjust for possible confounders: age, female sex, Acute Physiology and Chronic Health Evaluation (APACHE II) score, liver dysfunction, coagulopathy (international normalised ratio[INR] >1.5) and platelet counts of less than 100,000/uL).

Results: The study cohort included 276 patients from 14 participating adult ICUs, of whom 176 (63.8%) experienced dialysis dependence or death within 90 days of ICU admission (19 dialysis dependence, 157 death). Anticoagulation significantly reduced the odds of the primary outcome (adjusted odds ratio [AOR] 0.47, 95% confidence interval [CI] 0.27–0.83, *P*=0.009). Logistic regression analysis using anticoagulation as a 3-level indicator variable demonstrated that RCA was associated with mortality reduction (AOR 0.46, 95% CI 0.25–0.83, *P*=0.011), with heparin having a consistent trend (AOR 0.51, 95% CI 0.23–1.14, *P*=0.102).

Conclusion: Among critically ill patients with AKI, anticoagulation use during CKRT was associated with reduced dialysis or death at 90 days post-ICU admission, which was statistically significant for regional citrate anticoagulation and trended in the same direction of benefit for systemic heparin anticoagulation. Anticoagulation during CKRT should be considered whenever possible.

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Keywords: anticoagulation, critical care, kidney replacement therapy, mortality, nephrology

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CLINICAL IMPACT

What is New

- This is a large cohort study on continuous kidney replacement therapy (CKRT) practices in adult ICU patients.
- Two-thirds of patients with new onset acute kidney injury in ICU progress to develop chronic dialysis or death within 90 days of ICU admission.
- Mortality was highest amongst patients who did not receive anticoagulation with heparin or citrate.

Clinical Implications

- Anticoagulation during CKRT should be considered whenever possible.
- Future studies can be designed to look at the association of filter lifespan and efficiency with patient-centred outcomes, and the reasons for omitting anticoagulation.

INTRODUCTION

Acute kidney injury (AKI) affects 21.6% of critically ill adult patients,[1] with 5–7% requiring kidney replacement therapy (KRT).[2] AKI carries significant prognostic and socioeconomic implications—chronic kidney disease (CKD) progression over 1 year has been described in 21%, 30%, and 79% of initial survivors with septic AKI reversal, recovery and non-recovery, respectively.[3] AKI also increases the risk of developing end-stage kidney disease[4] leading to a significant healthcare and socioeconomic burden.[5] With the increasing incidence of AKI[6] and resultant end-stage kidney disease (ESKD), there has been increasing interest for effective treatment modalities, specifically therapies that might mitigate the rates of dialysis dependence.

Anticoagulation during continuous kidney replacement therapy (CKRT) prolongs the lifespan of the extra-corporeal circuit and optimal filter performance.[7] Regional citrate anticoagulation (RCA) is preferred due to filter running times; reduces bleeding complications; allows effective control of acid–base status; and reduces adverse events like heparin-induced thrombocytopenia (HIT).[8] The ideal anticoagulation strategy for CKRT remains debated,[9-11] with limited data on patient-centred outcomes such as eventual dialysis dependence or ICU mortality.[12] Heparin anticoagulation may not be feasible for patients who have ongoing bleeding manifestations or diathesis, or post-surgical patients in the early post-operative period.

Little is known about the contemporary KRT practices in Singapore.[13] Leveraging the collaboration with the Society of Intensive Care Medicine Singapore-National Investigators for Clinical Epidemiology and Research (SICM-NICER), we embarked on this study aiming to evaluate current trends, and the association of anticoagulation use on patient-centred outcomes. The primary outcome was dialysis dependence or death within 90 days of ICU admission.

METHOD

Study design and setting

We conducted a nationwide study in Singapore, a diverse nation of 5.7 million people. With 16 restructured hospitals and a range of specialised ICUs—including medical, surgical and subspecialty units (neurosurgical, cardiology and cardiothoracic)—our study covered the critical care landscape. This retrospective observational study encompassed all critically ill patients in participating adult ICUs across these restructured hospitals.

Study population

We included patients who had AKI and received CKRT between 1 April 2017 and 30 September 2017, and patients with ESKD were excluded. ESKD and AKI was defined as per the Kidney Disease Improving Global Outcomes (KDIGO) criteria.[14]

Data sources and definitions

We extracted details of the patients' KRT regimen and disease progression from electronic and paper medical records. At each individual site, patient details were collected and de-identified before being compiled by the principal investigator. Our analysis focused on the initial KRT session; specifically, only sessions with complete data were included. We excluded non-continuous modes of KRT such as intermittent haemodialysis, sustained low-efficiency dialysis (SLED) and peritoneal dialysis. All patients who received RCA for CKRT, received calcium-free dialysate and replacement solutions. Details about filter lifespan and performance were not collected. To quantify the degree of haemodynamic support, we utilised an inotrope score.[15] Liver dysfunction was defined as presence of liver cirrhosis or bilirubin (>35 μmol/L).[16] Coagulopathy was defined as INR>1.5, and thrombocytopenia was defined as platelet counts of <100,000/μL.

Statistical analysis

Continuous variables are presented as mean (standard deviation [SD]) and median (inter-quartile range [IQR]). Categorical variables are presented as number (%).

The initial KRT episode was analysed with multivariate logistic regression for factors associated with dialysis dependence or death at 90 days post-ICU (hyphen) admission. Logistic regression was done using key prognostic factors (i.e. age, female sex, APACHE II, liver dysfunction, coagulopathy, thrombocytopenia), and other possible confounders from Tables 1 and 2 with univariate *P* values of <0.05. Odds ratios were derived with 95% confidence intervals.

Ethics approval

Given the non-interventional nature of the study, waiver of informed consent was granted by the National Healthcare Group Domain Specific Review Board (DSRB reference 2017/01010) and mutually recognised by SingHealth Centralised Institutional Review Board (CIRB).

RESULTS

A total of 14 ICUs across 6 hospitals in Singapore contributed data to the study. The study population is described in Fig. 1. A total of 867 patients received KRT during the study period. The characteristics of 276 patients were analysed, and characteristics of their ICU stay, are described in Table 1. The most common cause of AKI was in association with sepsis, and the median ICU length of stay (LOS) was 7 days. In total, 176 patients (63.8%) experienced dialysis dependence or death within 90 days of ICU admission (19 dialysis dependence, 157 death).

Continuous veno-venous hemodiafiltration (CVVHDF) was the top choice for initial CKRT mode, accounting for 62% of sessions. Other modes included continuous veno-venous hemodialysis (CVVHD) (19.6%), continuous veno-venous hemofiltration (CVVH) (17.0%), and slow continuous ultrafiltration (SCUF) (1.1%). Table 2 provides further details on the characteristics of the CKRT sessions. The median time to first circuit change was 455.0 minutes (IQR 8.0–1192.0 minutes). Circuit changes were done for various reasons such as interruptions of CKRT for procedures, refractory haemodynamic instability, or circuit clotting or clogging.

Among the 276 patients receiving CKRT, anticoagulation during the first CKRT session during the ICU admission was associated with reduction of dialysis dependence and mortality at 90 days (adjusted OR [aOR] 0.47, 95% CI (0.27–0.83), *P*=0.009) (Table 3). Repeating the logistic regression analysis using anticoagulation as a 3-level indicator variable, demonstrated that citrate anticoagulation was associated with mortality reduction (aOR 0.46, 95% CI 0.25–0.83, *P*=0.011) and with heparin having a consistent trend (aOR 0.51, 95% CI 0.23–1.14, *P*=0.102), compared to no anticoagulation use. In contrast, liver dysfunction, coagulopathy and thrombocytopenia did not have significant independent associations of dialysis dependence or death at 90 days.

DISCUSSION

This is the largest-ever observational study of AKI patients undergoing CKRT in Singapore. Among ICU patients who suffered AKI, 63.8% were left with dialysis dependence or died within 90 days. Mortality was highest in patients who did not receive anticoagu-lation with either heparin or citrate, and citrate anticoagulation was associated with reduced mortality. Heparin anticoagulation showed a consistent trend with the odds ratio in the same direction as citrate anticoagulation, but did not similarly reach significance, likely due to the smaller sample size for heparin (n=46), compared to citrate anticoagulation (n=100).

Sepsis was the leading cause of AKI in our study, in keeping with international data.[2] The 90-day mortality rate of 43.1% is consistent with international studies[2] as well and underscores the high mortality rate of AKI. The most common mode of CKRT in Singapore was CVVHDF, which is consistently favoured in published literature because of its lower failure rate compared to other modalities of CKRT.[17] This is comparable with patients who had AKI who received SLED.[18]

Comparing between patients who had anticoagulation during KRT against those who did not (Table 1), there were more patients in the group that did not receive anticoagulation with platelet counts <100,000/μL. This could be a biomarker for bleeding risk. However, after adjusting for it during multivariable analysis, anticoagu-lation use retained a significant association with the primary outcome. There were differences in the prescribers who chose anticoagulation and those who omitted anticoagulation, but this may just reflect anticoagulation preference, rather than expertise with renal care. We therefore did not adjust for it in multiva-riable analysis.

Patients in the group receiving anticoagulation had higher numbers with hypokalemia and hypophosphatae-mia. This may be due to regional citrate anticoagulation, but we did not adjust for these as complications did not precede exposure to anticoagulation. The number of re-placement or dialysate fluid bags were different between groups. However, we did not adjust for this as this did not precede exposure to anticoagulation.

Table 1. Patient demographics and ICU stay characteristics.

Variables	All patients n=276	Patients not on anticoagulation n=130	Patients on anticoagulation n=146	*P* value
Demographics				
Age, meanSD, years	64.2±13.8	64.5±14.2	63.8±13.4	0.663
Female, n (%)	104 (37.7)	48 (36.9)	56 (38.4)	0.901
BMI mean±SD, kg/m^2	25.0±7.7	24.5±5.3	25.5±9.3	0.318
Comorbidities^				
Diabetes mellitus, n (%)	147 (53.3)	60 (46.2)	87 (59.6)	0.030
Hypertension, n (%)	191 (69.2)	87 (66.9)	104 (71.2)	0.514
Ischaemic heart disease, n (%)	96 (34.8)	44 (33.9)	52 (35.6)	0.801
Chronic kidney disease, n (%)	111 (40.2)	45 (34.6)	66 (45.2)	0.085
COPD, n (%)	15 (5.4)	8 (6.2)	7 (4.8)	0.791
Cancer, n (%)	38 (13.8)	20 (15.4)	18 (12.3)	0.488
Liver dysfunction,* n (%)	123 (44.6)	63 (48.5)	60 (41.1)	0.228
Coagulopathy,** n (%)	32 (11.6)	20 (15.4)	12 (8.2)	0.089
Thrombocytopenia,*** n (%)	78 (28.3)	45 (34.6)	33 (22.6)	0.032
Cause of AKI				0.151
Sepsis, n (%)	151 (54.7)	67 (51.5)	84 (57.5)	
Hypovolemia/ shock, n (%)	21 (7.6)	15(11.5)	6 (4.1)	
Nephrotoxic agents, n (%)	4 (1.4)	2 (1.5)	2 (1.4)	
Major surgery, n (%)	16(5.8)	7 (5.4)	9 (6.2)	
Hepatorenal syndrome, n (%)	10 (3.6)	8 (6.2)	2 (1.4)	
Cardiogenic shock, n (%)	55(19.9)	24 (18.5)	31 (21.2)	
Post-obstructive, n (%)	2 (0.7)	1 (0.8)	1 (0.7)	
Others (e.g. rhabdomyolysis, pancreatitis), n (%)	17 (6.2)	7 (5.4)	10 (6.8)	
Admission source				0.199
Emergency department, n (%)	118 (42.8)	55 (42.3)	63 (43.2)	
General ward, n (%)	99 (35.9)	43 (33.1)	56 (38.4)	
Operating theatre, n (%)	29 (10.5)	13 (10.0)	16 (11.0)	
High dependency unit/ intermediate care unit, n (%)	19 (6.9)	14 (10.8)	5 (3.4)	
Others (e.g. endoscopy suite), , n (%)	11 (4.0)	5 (3.8)	6 (4.1)	
APACHE II score, mean±SD	27.3±9.5	28.49.8	26.4±9.3	0.091
Vasopressor use, n (%)	221 (80.1)	109 (83.8)	112 (76.7)	0.181
Inotrope score, mean±SD	3.2±2.0	3.4±2.0	3.0±2.0	0.079
Respiratory support received before CKRT				
HFNC, n (%)	19 (6.9)	10 (7.7)	9 (6.2)	0.640
NIV, n (%)	34 (12.3)	20 (15.4)	14 (9.6)	0.479
Mechanical ventilation, n (%)	236 (85.5)	118 (90.8)	118 (80.8)	0.019
ICU LOS (days), median (IQR)	7 (3-16)	6.5 (3-16)	7 (3-17)	0.982
Survival				
Survived ICU stay, n (%)	152 (55.1)	56 (43.1)	96 (65.8)	<0.001
Survived at 30 days of ICU admission, n (%)	133 (48.2)	50 (38.5)	83 (56.9)	0.003
Survived at 90 days of ICU admission, n (%)	119 (43.1)	43 (33.1)	76 (52.1)	0.002
Mechanical ventilation free days up to 28 days, mean±SD	11.4±12.2	10.4±11.8	12.3±12.4	0.217
Fluid balance 24 hours prior to KRT (mL), median (IQR)	1291.2 (580.5-2258.0)	1321.50 (636.9- 2440.3)	1090.0 (434.8-2109.2)	0.479
Duration of oliguria before KRT, median (IQR)	10.0 (2.3-20)	12 (6-24)	10 (0-18)	0.381
Peak creatinine prior to KRT, μmol/L, median (IQR)	298 (214-489)	286.5 (200-465)	313 (219-514)	0.070

^Patients may have more than 1 comorbidity
AKI: acute kidney injury; CKRT: continuous kidney replacement therapy; COPD: chronic obstructive pulmonary disease; HFNC: high-flow nasal cannula; ICU: intensive care unit; INR: international normalised ratio; IQR: interquartile range; LOS: length of stay; NIV: non-invasive ventilation, PTT: partial thromboplastin time; SD: standard deviation
*Liver dysfunction (defined as presence of liver cirrhosis or bilirubin >35 μmol/L)
**INR>1.5
***Platelet <100,000/μL

Table 2. Characteristics of continuous kidney replacement therapy (CKRT) sessions.

Variables	All patients n=276	Patients not on anticoagulation n=130	Patients on anticoagulation n=146	*P* value
Type of anticoagulation, n(%)				NA
None	130 (47.1)	130	0	
Regional citrate	100 (36.2)	0	100	
Systemic heparin	46 (16.6)	0	46	
Prescription, n (%)				<0.001
Renal physician	108 (39.1)	81 (62.3)	27 (18.5)	
Intensivist	139 (50.3)	43 (33.1)	96 (65.8)	
Others	29 (10.5)	6 (4.6)	23 (15.7)	
Indication,^ n (%)				
Routine / regular session	9 (3.3)	4 (3.1)	5 (3.6)	1.000
Clearance of toxins	3 (3.2)	2 (1.5)	1 (0.7)	0.603
Rhabdomyolysis	13 (4.7)	9 (6.9)	4 (2.7)	0.153
Hyperkalemia	96 (34.8)	47 (36.2)	49 (33.5)	0.705
Acidosis	200 (72.5)	92 (70.8)	108 (74.0)	0.591
Fluid overload	70 (25.4)	26 (20.0)	44 (30.1)	0.071
Uraemia	45 (16.3)	19 (14.6)	26 (17.8)	0.516
Oligo-anuria	206 (74.6)	87 (66.9)	119 (81.5)	0.006
Timing of KRT, n (%)				
After office hours	158 (57.2)	73 (56.2)	85 (58.2)	0.808
Duration of first CKRT (hours), median (IQR)	19.5 (8.3-35.0)	19.0 (6.0-34.0)	20.0 (10.0-34.0)	0.840
Time to first circuit change (min), median (IQR)	455.0 (8.0-1192.0)	585.0 (120.0-1475.0)	165.0 (0-879.8)	0.096
Complications after CKRT,^ n (%)				
Hypokalemia	67 (24.3)	19 (14.6)	48 (32.9)	<0.001
Hypophosphataemia	64 (23.2)	21 (16.2)	43 (29.5)	0.017
Bleeding complications	38(13.8)	15 (11.5)	23 (15.8)	0.382
Arrhythmia	103 (37.3)	51 (39.2)	52 (35.6)	0.553
Prescribed dose for CKRT (ml/kg/hour), median (IQR)	33.3 (30.0-35.0)	33.0 (30.0-35.0)	35.0 (30.0-35.0)	0.096
Number of replacement/dialysate fluid bags				
Bag 1, median (IQR)	6.0 (3.0–12.0)	5.0 (2.0–13.0)	7.0 (3.0–11.0)	0.067
Bag 2, median (IQR)	4.0 (2.0–7.0)	4.0 (1.0–5.0)	4.0 (2.0–7.0)	0.031

^May have more than 1 per session
KRT: Kidney replacement therapy; SD: standard deviation

There were more patients in the anticoagulation group with oligo-anuria than patients who did not receive anticoagulation, though the reason for this is unclear. Nonetheless, we adjusted for this and anticoagulation used remained significantly associated with the primary outcome. Oligo-anuria preceding CKRT was found to be an adverse prognostic factor (Table 3), consistent with a large series that showed it was an independent risk factor for death or end-stage kidney disease in AKD patients.[19] These could be due to less morphologic and functional damage in non-oliguric compared with oliguric AKI (found in animal studies[20]), and the absence of oliguria in AKI reflects less severe disease.[21]

Anticoagulation in some form is recommended during CKRT to prolong filter lifespan, because problems with filter clotting will lead to interruptions to CKRT and may result in loss of blood which is in the circuit. Ideally, CKRT should be prescribed with anticoagulation. However, in critically ill patients, this is often contraindicated due to bleeding diathesis, recent surgery precluding use of heparin, or liver failure precluding the use of regional citrate anticoagulation, which will lead to metabolic acidosis and reduced ionised calcium. In severely critically ill patients, disease-induced coagulopathy or thrombocytopenia may also render anticoagulation unnecessary.

With regard to medical contraindications, patients in our study did not have statistically significant differences in the presence of liver dysfunction or coagulopathy, but there were more with thrombocytopenia (platelet counts <100,000/μL) in the group that did not receive anticoagulation.

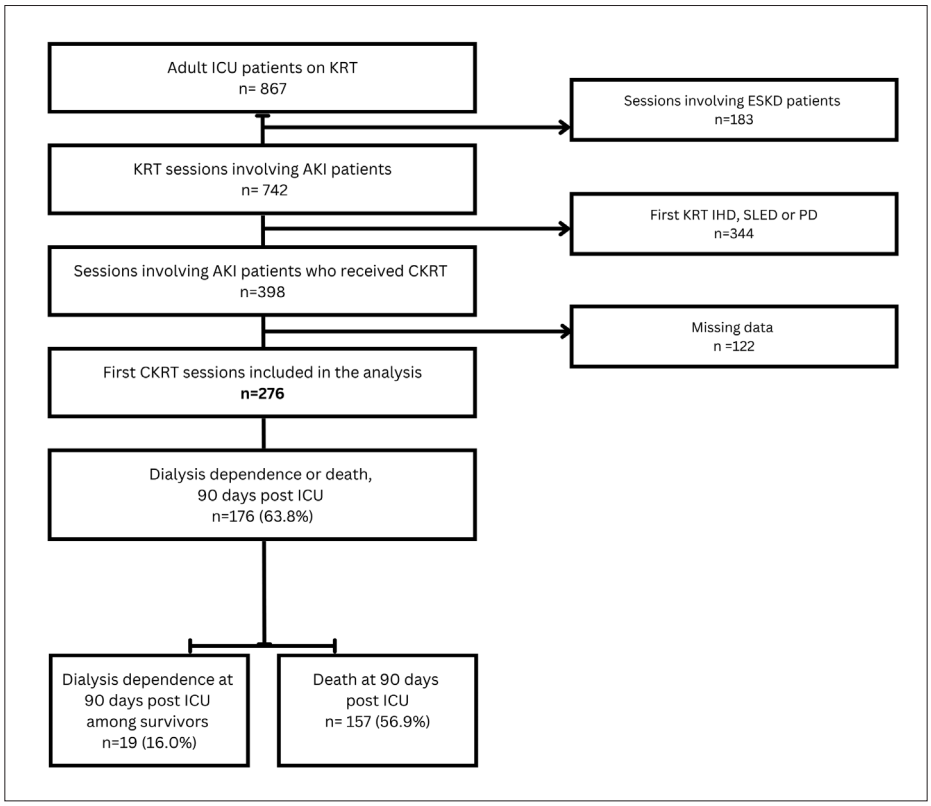

Figure 1. Study population flowchart.
AKI: acute kidney injury; KRT: kidney replacement therapy; CKRT: continuous kidney replacement therapy; ESKD: end stage kidney disease; IHD: Intermittent hemodialysis, SLED: slow low efficiency dialysis, PD: peritoneal dialysis

Table 3. Multivariable logistic regression of factors associated with dialysis dependence or death at 90 days post intensive care unit admission.

Dialysis dependence or death at 90 days	Odds ratio	95% CI of odds ratio	*P* value
Age	1.01	0.99-1.03	0.550
Female	1.19	0.69-2.05	0.539
APACHE II	1.03	1.00-1.07	0.034
Liver dysfunction*	1.30	0.76-2.21	0.340
Coagulopathy**	1.05	0.68-1.63	0.827
Thrombocytopenia***	0.86	0.47-1.57	0.626
Diabetes mellitus	0.96	0.72-1.28	0.777
Mechanical ventilation	1.90	0.89-4.06	0.097
Oliguria and anuria	2.95	1.59-5.50	0.001
Anticoagulation	0.47	0.27-0.83	0.009
Anticoagulation as a 3-level indicator variable			
No anticoagulation	Reference	Reference	Reference
Heparin anticoagulation	0.51	0.23-1.14	0.102
Citrate anticoagulation	0.46	0.25-0.83	0.011

APACHE II: Acute Physiology and Chronic Health Evaluation II; CI: confidence interval
*Liver dysfunction (defined as presence of liver cirrhosis or bilirubin >35 μmol/L)
** INR >1.5
*** Platelet <100,000/μL

We can postulate the reasons why prescribers omit anticoagulation in the initial KRT session. Patients are acutely ill with organ failure, thus the preference to avoid systemic anticoagulation to not increase bleeding risks and to avoid regional citrate anticoagulation to minimise pH and electrolyte changes (e.g. calcium, magnesium and phosphate). Regional citrate anticoagulation (RCA) also requires familiarity with the protocol and logistically poses more challenges.

Interruptions to CKRT impact on physiological stability, patient treatment, with added costs. The literature consistently shows RCA is beneficial for filter lifespan, with lower adverse events, compared to heparin anticoagulation.[10] Despite this, the evidence for anticoagulation strategies and impact on mortality is not strong,[22] and still being investigated. For instance, in one previous study, there was no difference in mortality, metabolic alkalosis, circuit loss and the amount of blood transfused between patients with heparin anticoagulation and RCA.[23]

One of the postulated reasons for the findings is that anticoagulation had a beneficial impact on filter efficacy,[24] as delivered dose is reported to be highest in treatments where RCA was employed, with lower odds of death compared to CKRT with heparin anticoagulation.[24]

However, we are unable to detect this association as this study did not collect data on filter efficacy by calculating effluent urea nitrogen/blood urea nitrogen ratios. We also did not specifically study filter lifespan or distinguish between interruptions to initial CKRT due to filter performance or extrinsic factors (such as need for interventions).

The strength of this study is that data were obtained from mixed, surgical, cardiac and medical units, which increases the generalisability of the data. This is also the first period prevalence study showing anticoagulation practices during CKRT in Singapore.

The limitations of this study are that it was a retrospective study, which was dependent on existing clinical databases, and thus there were missing or incomplete data. Not all units in Singapore participated in the study due to logistical reasons, but all tertiary hospitals are represented in this data. We also did not consider subsequent KRT sessions the patients received, which may have contributed to the prognosis. However, the initial KRT sessions early in AKI and critical illness may pose the highest risk, whereas subsequent sessions may be routine KRT while awaiting kidney recovery and have less prognostic impact. Other conditions that contraindicate anticoagulation may have led to the primary outcome, but we have adjusted for illness severity, liver dysfunction and thrombocytopenia, and they were all not found to be associated with the primary outcome.

Anticoagulation during CKRT should be considered whenever possible. However, there are non-anticoagulant factors such as type and location of vascular access, blood flow rates and haematological conditions that influence filter efficiency and lifespan[17]; and anticoagulation is just one factor influencing filter performance. Future studies can consider studying specifically filter duration and efficiency and take into consideration all KRT sessions received by the patient. Future studies should also investigate other physician considerations for not using anticoagulation.

CONCLUSION

Among critically ill patients with AKI, anticoagulation use during CKRT was associated with reduced dialysis or death at 90 days post-ICU admission, which was statistically significant for regional citrate anticoagulation and trended in the same direction of benefit for systemic heparin anticoagulation. Anticoagulation during CKRT should be considered whenever possible.

Disclosure

The authors have no relevant financial or non-financial interests to disclose.

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ORIGINAL ARTICLE

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Plasma selenium and zinc alter associations between nephrotoxic metals and chronic kidney disease: Results from NHANES database 2011–2018

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ABSTRACT

Introduction: Chronic kidney disease (CKD) is a condition defined as a persistent change in kidney structure or function, or both, that compromises human health. Environmental exposure to heavy metals (e.g. cadmium, lead, arsenic and mercury) is common, and high exposure levels are known to cause nephrotoxicity. Micronutrients such as selenium and zinc are positively associated with better kidney function and renal outcomes. This study determined the associations between CKD and heavy metal exposures measured in blood or urine within a community-dwelling population, and assessed whether and how selenium and zinc modified the associations.

Method: Data were extracted from 4 cycles of the US National Health and Nutrition Examination Survey (NHANES) database (2011–2012, 2013–2014, 2015–2016 and 2017–2018).

Results: Univariate analysis showed that higher quartiles of plasma lead and cadmium concentration were more likely associated with CKD than the lowest quartile, and along with folate, were linked to greater odds of CKD. Conversely, as plasma selenium and serum zinc increased, the odds of CKD decreased. Multivariate analysis had similar results after adjusting for relevant confounders. Higher plasma cadmium quartiles were associated with higher odds of CKD. Associations between higher quartiles of plasma selenium and serum zinc were significantly associated with lower odds of CKD.

Conclusion: Elevated blood levels of heavy metals increase CKD, whereas elevated concentrations of plasma selenium and serum zinc decrease CKD. A high serum zinc concentration appears to interact with low-toxicity heavy metals to reduce CKD risk. This study suggests that increased selenium and zinc in the body along with avoidance of heavy metal exposures could protect against CKD.

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Keywords: arsenic, cadmium, chronic kidney disease, CKD, lead, mercury, National Health and Nutrition Examination Survey, NHANES, selenium, zinc

INTRODUCTION

Chronic kidney disease (CKD) is a clinical condition comprising persistent changes in kidney function or structure, or both. It is characterised by irreversible and progressive evolution, increasing the risk of complications and mortality. As the 16th leading cause of mortality worldwide, CKD affects 8–16% of the global population.[1,2] Clinically, CKD is classified by albuminuria (an indicator of glomerular damage) and the glomerular filtration rate (GFR) (a well-established marker of renal excretory function). Both are considered reliable predictors of the outcomes of long-term CKD.[3] In CKD, GFR <60 mL/min/1.73 m^2 or proteinuria ≥30 mg/24h for more than 3 months indicates persistent renal structural or functional abnormalities.[4] CKD is divided into 5 stages according to GFR and 3 steps according to proteinuria. The staging system helps to determine the monitoring method and intensity of CKD. Prognostic factors include age, sex, race, plasma cholesterol concentration and smoking. Adverse outcomes associated with CKD include death and end-stage renal disease (ESRD),[5] which may

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CLINICAL IMPACT

What is New

- This study highlights the protective effects of micronutrients against chronic kidney disease (CKD) among patients who have high blood levels of heavy metals.
- Higher blood cadmium levels significantly increased the risk of CKD.
- Conversely, the elevation of serum selenium and zinc neutralised toxic heavy metals consisting of lead, cadmium and mercury. The incidence of CKD was decreased.

Clinical Implications

- Increasing the blood concentrations of selenium and zinc as well as avoiding heavy metal exposures might help to prevent the development of CKD.
- The accumulation of selenium and zinc appears to alleviate the damage caused by heavy metals to the kidneys.

be prevented through proper clinical diagnosis and management.[6]

Global industrialisation continues to meet the needs of modern humans, but the associated costs include substantial pollution of the environment with various toxic pollutants, including heavy metals.[7] The accumulation of toxic heavy metals in the environment may have deleterious effects on human health.[8] Heavy metals are classified as those that have high atomic mass in the range of 63.5–200.6 daltons.[9] Environmental heavy metal exposures, including those of cadmium, lead, arsenic and mercury, are common, and high exposure levels in certain populations are recognised as nephrotoxic.[10-12] Other heavy metals might also harm the body when they exceed specific thresholds, although the toxic levels of heavy metals are affected by many factors, such as exposure route, dose and oxidative status, in addition to human factors, such as age, genetics, sex and dietary status.[13] Toxic heavy metals are prevalent nephrotoxicants that unfortunately, have not been fully studied in humans.

A previous study reported an association between certain heavy metals and kidney disease, which was largely explained by toxic effects on proximal tubular function.[14] A case-controlled study with a population-based cohort found an association between red blood cell (RBC) lead levels and an increased risk of ESRD.[15] While the toxic effects of heavy metals are deleterious to humans, micronutrients are essential for maintaining normal human physiology. Micronutrients such as selenium, zinc and folic acid are positively associated with better renal outcomes and kidney function.[16]

Several protective mechanisms of selenium and zinc against metal toxicity in animals and cells have previously been reported.[17] Even dysregulation of metal or trace-metal homeostasis in biological systems can lead to severe deleterious effects in many diseases.[18] However, the combined effects of environmental heavy metal exposures measured in human bodies and micronutrients such as selenium, zinc and folate on CKD and renal function remain to be assessed. This study aimed to investigate the associations between CKD and heavy metal exposures measured in the urine or blood among the general community-dwelling population, and whether and how selenium and zinc modified the associations.

METHOD

Study design and data source

This cross-sectional retrospective cohort study extracted all patient data from National Health and Nutrition Examination Survey (NHANES) database collected by National Center for Health Statistics (NCHS) of US Centers for Disease Control and Prevention. The survey assesses US children and adults' health and nutritional status, using a complex, multistage design to collect and analyse the data representative of US national non-institutionalised population. Data are released on a biennial cycle for research purposes, and NCHS permits researchers to use the data. Participants in NHANES complete home interviews and are invited to undergo an extensive examination at NHANES Mobile Examination Center, including physical examinations, speciality measurements and laboratory tests. Thus, participants' assessments in NHANES database are robust and multidimensional and can be equated to population-level estimates.[19]

Study population

All data were extracted from 4 released 2-year cycles in the NHANES database (2011–2012, 2013–2014, 2015–2016 and 2017–2018), for a total of 8 years. Adults aged 18 years or older, who had complete information of the variables of interest, were eligible for inclusion. Subjects with ESRD, defined as an estimated GFR (eGFR) of <15 mL/min/1.73 m^2, and

participants without eGFR data were excluded. The included population was divided into participants with or without CKD, defined as having an eGFR <60 mL/min/1.73 m^2 for further comparisons.

The NCHS Research Ethics Review Board approved NHANES.

Data collection

Assessment of CKD

Creatinine measurements were obtained from standardised biochemical profiles collected by NHANES for each participant. The Beckman Synchron LX20 Modular Chemistry Analyzer (Beckman Coulter, Indianapolis, IN, US) used the Jaffe rate method (kinetic alkaline picrate) to determine creatinine concentrations in urine, serum or plasma. GFR was estimated from recalibrated serum creatinine using the 4-variable Modification of Diet in Renal Disease (MDRD) study equation. Isotope dilution mass spectrometry traceable MDRD study equation using standardised creatinine: GFR = 175 × (standardised serum creatinine)$^{-1.154}$ × (age)$^{-0.203}$ × 0.742 (for female participants) × 1.212 (for African American) was applied.[20] Estimated GFR is reported in mL/min/1.73 m^2. CKD was defined by an eGFR of less than 60 mL/min/1.73 m^2.

Assessment of blood lead, cadmium, mercury and urinary arsenic

Blood samples were processed, frozen at -20 °C and sent to the Centers for Disease Control and Prevention's National Center for Environmental Health (NCEH), US for testing. Detailed descriptions of the laboratory methods used by NHANES can be found on the NHANES website. Whole blood was analysed for cadmium, mercury, lead and total urinary arsenic by inductively coupled plasma dynamic cell reaction mass spectrometry (ICP-MS) in the Laboratory Sciences Division of the NCEH.[21] Urine creatinine concentration was determined as a marker of urine dilution and was selected by Jaffe rate response using a Beckman Synchron Analyzer LX20 Modular Chemistry Analyzer (Beckman Coulter, Indianapolis, IN, US).

Assessment of plasma selenium, serum zinc and serum folate

Briefly, cyclic selenium was tested in the trace element laboratory using ICP-MS.[21] Serum zinc was measured using the same method as the other trace metals in the same facility.[22] Microbiological assays measure whole-blood folate, whereas serum folate is measured by isotope dilution high-performance liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS). RBC folate was then calculated using data from both assays.

Covariates

Demographic data, including age, race, sex, education level and household income-to-poverty ratio, were obtained through face-to-face interviews conducted by trained interviewers using the Household and Sample Demographic Questionnaire and the Computer-Assisted Personal Interviewing system. Collected data were weighted according to the NHANES protocol.

Body mass index (BMI) values were obtained from NHANES examination measurements for anthropomorphic data and calculated as weight in kg divided by height in m^2. Included participants were split into underweight (<18.5 kg/m^2), average (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2) and obese (≥30.0 kg/m^2) according to their BMI. For smoking status, participants were categorised as never smokers, exposed to ambient tobacco smoke, or active smokers. Active smokers were defined as having smoked >100 cigarettes in their lifetime and answering "yes" to the question: "Do you smoke now?" or having a serum cotinine level >10 μg/L (ng/mL). Exposure to environmental tobacco smoke was defined as detectable serum cotinine of 0.015, but not more than 10 μg/L (ng/mL). Non-smokers smoked fewer than 100 cigarettes in their lifetime or had a serum cotinine level <10 μg/L (ng/mL). Alcohol consumption was categorised based on responses to survey questions defining alcohol consumption, including excessive drinking, characterised by a reply ≥4 times per week to the following question: "In the past 12 months, how often did you drink an alcoholic beverage?" Vigorous physical activity was determined based on individuals' self-reported vigorous physical exercise versus no physical activity in the past 30 days.

High blood pressure was defined by those who answered "yes" to the following questions or met the criteria: "Have you been told on 2 or more different visits that you have hypertension, also known as high blood pressure?" or "Because of your hypertension, have you ever been told to take prescription medications?" or have a mean systolic blood pressure of ≥140 mmHg over 3 consecutive measurements or have a mean diastolic blood pressure of over 3 straight steps ≥90 mmHg. The following questions and criteria define diabetes: "Apart from pregnancy, have you ever been told by a doctor or a health professional that you have

diabetes or sugar diabetes?" or "Are you currently taking insulin?" or "Are you currently taking diabetes medication to lower blood glucose, sometimes called oral antidiabetic medications?" or have HbA1c of ≥6.5% (≥48 mmol/mol) or laboratory-measured fasting blood glucose >125 mg/dL (6.94 mmol/L). Hyperlipidaemia was defined as a self-reported answer "yes" to the question or met the criteria: "Have you ever been told by a doctor or a health professional to take a prescription drug to lower blood cholesterol?" or have a total cholesterol level of >200 mg/dL (5.20 mmol/L). History of cardiovascular disease, including coronary heart disease, angina, congestive heart failure, myocardial infarction and stroke, was defined by the question: "Has a doctor or a health professional ever told you that you have (disease)?" Chronic obstructive pulmonary disease (COPD) is described as positive responses to the questions: "Has a doctor or a health professional ever told you that you have emphysema?" or "Has a doctor or a health professional ever told you that you have chronic bronchitis?"

Statistical analysis

Statistical analysis was performed using SAS statistical software, version 9.4 (SAS Inc, Cary, NC, US). NHANES draws samples from a complex sampling scheme that combines variables from different study periods. Using sample weights provided by NHANES, it is possible to estimate the equivalent total number of individuals in the whole country from the study sample. Continuous variables are presented as means and standard errors (SE), and categorical variables are presented as unweighted numbers and weighted proportions. Differences in means between groups were compared using the SURVEYREG procedure for continuous variables. Rao-Scott chi-square tests were also performed on categorical variables using the SURVEYFREQ programme to examine differences in proportions between groups. Logistic regression was performed using the SURVEYLOGISTIC procedure to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for associations between prevalent CKD and study variables. Variables that reached statistical significance in univariate analysis were entered into multivariate models for adjustment. A 2-sided *P* value <0.05 was determined to be statistically significant. Three types of associations were assessed. First, roughly linear associations between $\log_{10}$ GFR and blood lead, cadmium, mercury, urinary arsenic, plasma selenium, serum zinc, serum and erythrocyte folate levels. Second, presence of CKD with blood metals, crude and adjusted associations between urinary arsenic, plasma selenium, serum zinc, serum and erythrocyte folate quartiles. Third, quartile cut-off values were determined by the distribution of data across all subjects for combined effects of blood metals, urinary arsenic and plasma selenium or serum zinc on CKD. In a combined effects analysis, "high" levels represent the highest quartile (Q4), whereas "low" levels represent the lowest quartile (Q1).

RESULTS

Study sample selection

The flow diagram of study participants' inclusion and exclusion is presented in Fig. 1. The sample data were extracted from the 4 released cycles of the NHANES database. A total of 39,156 participants identified as eligible, and 23,825 patients aged >18 years were selected. Individuals with ESRD or those with no eGFR results were excluded, leaving 21,251 participants. Finally, 9557 subjects with laboratory measures of heavy metals and micronutrients of interest were included as the primary cohort for the subsequent analysis. Sample weights were assigned to each sampled individual by NHANES for calculating the equivalent population size in the entire US. After weighting, the cohort size (n=9557) was equivalent to 236,263,413 community-dwelling adults of the US (Fig. 1).

Study population characteristics

Blood and urine measures, demographic characteristics, lifestyle and comorbid conditions of the study population

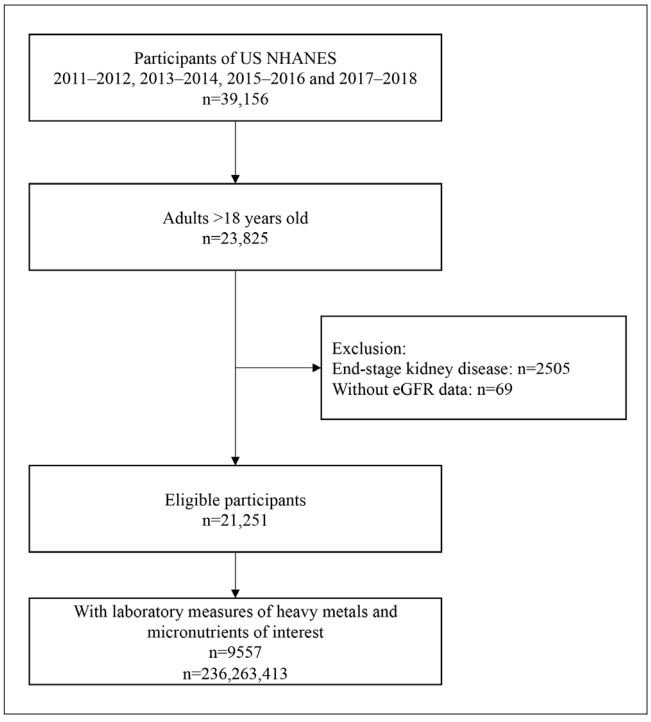

Fig. 1. Flow diagram of study sample selection.

with or without CKD are summarised in Table 1. The mean age of the study cohort was 46.7 ± 0.03 years, and 51.5% were females. Most participants were non-Hispanic whites (64.4%) and non-smokers (57.0%). The most common comorbid conditions of the study cohort were hyperlipidaemia (52.0%) and hypertension (34.7%). Regardless of being continuous variables or categorised in quartiles, blood lead, plasma selenium, serum folate and RBC folate showed significantly different distributions between participants with or without CKD. Significant differences in distribution were noted in blood cadmium levels in quartiles between subjects with or without CKD. Blood mercury, as a continuous variable, also showed differences between CKD and non-CKD participants. Significant differences were found in all other variables, except for education level and excessive alcohol consumption between individuals with and without CKD (Table 1).

Associations between selenium, zinc, folate, lead, cadmium, mercury, arsenic levels and prevalent CKD

Crude associations between log transformed eGFR and levels of plasma selenium, zinc, serum folate and RBC folate are shown in Fig. 2. Serum zinc was positively associated with $\log_{10}$ eGFR with β (SE) 2.1 (1.4) μg/dL, P=0.160. However, blood selenium with β (SE) -1.1 (1.9) μg/L, P=0.578, serum total folate with β (SE) -6.9 (1.2) μg/L (ng/mL), P<0.001, and RBC folate with β (SE), -136.3 (20.7) ng/mL, P<0.001) were inversely associated with $\log_{10}$ eGFR (Fig. 2).

Crude associations between log-transformed eGFR and levels of blood lead, cadmium, mercury and urine arsenic are illustrated in Fig. 3. Urine arsenic was positively associated with $\log_{10}$ eGFR with β (SE) 1.2 (2.7) μg/L, P=0.649. Blood lead with β (SE) -0.5 (0.1) μg/dL, P<0.001, cadmium with β (SE) -0.04 (0.04) μg/L, P=0.332, and total mercury in blood with β (SE) -0.005 (0.098) μg/L, P=0.961 were inversely associated with $\log_{10}$ eGFR (Fig. 3).

The associations between levels of blood lead, cadmium, mercury, plasma selenium, serum folate, RBC folate, serum zinc in quartiles and prevalent CKD are summarised in Table 2. Univariate analysis showed greater odds for CKD compared to the lowest quartile (Q1) and higher quartiles (Q2–Q4) of blood lead and cadmium. In addition, serum and RBC folate in the highest quartile (Q4) were associated with greater odds for CKD. Decreased odds for CKD were associated with increasing plasma selenium and serum zinc (Q2–Q4). Multivariable analysis maintained these results after adjusting for relevant confounders. Compared to Q1, higher blood cadmium quartiles were associated with greater odds for CKD (adjusted OR [AOR] 1.93, 95% CI 1.25–3.00 for Q3; AOR 2.79, 95% CI 1.58–4.92 for Q4). For plasma selenium and serum zinc, statistically significant associations were noted between higher quartiles (vs Q1) and lower odds for CKD (Table 2).

Combined effects of selenium and zinc with blood lead, cadmium, mercury and urine arsenic on CKD risk

After adjusting for relevant confounders in multivariable analysis, high selenium and low cadmium was associated with significantly reduced odds for CKD (AOR 0.23, 95% CI 0.07–0.72) compared to low selenium and high cadmium. High zinc with either high lead or low lead was associated with significantly lower odds for CKD (AOR 0.10, 95% CI 0.03–0.33 for high zinc and high lead; AOR 0.08, 95% CI 0.01–0.65 for high zinc and low lead) compared to low zinc and high lead. Similarly, compared to low zinc and high cadmium, high zinc with either high or low cadmium was associated with significantly lower odds for CKD (AOR 0.10, 95% CI 0.02–0.43 for high zinc and high cadmium; AOR 0.11, 95% CI 0.02–0.76 for high zinc and low cadmium). In addition, compared to low zinc and high mercury, high zinc with either high or low mercury was associated with significantly lower odds for CKD (AOR 0.15, 95% CI 0.02–0.97 for high zinc and high mercury; AOR 0.09, 95% CI 0.02–0.58 for high zinc and low mercury) (Table 3).

DISCUSSION

This study investigated associations between CKD and heavy metal exposure measured in the blood or urine of a general community-based population. It also determined whether and how selenium and zinc might alter the associations, using the comprehensive data of 4 cycles of NHANES.

Findings showed that elevated plasma selenium and serum zinc interact with low-toxicity heavy metals to reduce odds of CKD, suggesting that increasing selenium or zinc levels and avoiding heavy metal exposures may help protect against developing CKD. Subjects with higher blood cadmium levels had significantly increased likelihood of CKD, whereas those with higher level of plasma selenium or serum zinc had significantly reduced CKD risk. Regarding combined effects, high serum zinc strongly reduced the likelihood of CKD among those who had high blood lead, high cadmium and high mercury levels, suggesting that zinc can modify the harm posed by heavy metals on the kidneys.

Table 1. Blood and urine parameters, demographic characteristics, lifestyle and comorbid conditions of the study population with or without CKD.

Variables	Overall[a] (n=9557)	CKD		*P* value
		No (n=8845)	Yes (n=712)	
Blood lead, mean ± SD, µg/dL	1.3 ± 0.04	1.2 ± 0.04	1.5 ± 0.1	**<0.001**
Q1 (≤0.6)	1712 (26.6)	1665 (27.6)	47 (11.4)	**<0.001**
Q2 (>0.6–1.0)	1861 (27.9)	1759 (28.3)	102 (21.5)	
Q3 (>1.0–1.6)	1803 (24.4)	1642 (23.8)	161 (31.9)	
Q4 (>1.6)	1728 (21.2)	1519 (20.2)	209 (35.2)	
Missing	2453	2260	193	
Blood cadmium, mean ± SD, µg/L	0.5 ± 0.01	0.5 ± 0.01	0.5 ± 0.04	0.323
Q1 (≤0.2)	2107 (34.6)	2040 (36.0)	67 (13.9)	**<0.001**
Q2 (>0.2–0.3)	1397 (20.5)	1301 (20.6)	96 (19.6)	
Q3 (>0.3–0.6)	1969 (24.8)	1761 (23.6)	208 (41.9)	
Q4 (>0.6)	1631 (20.1)	1483 (19.7)	148 (24.6)	
Missing	2453	2260	193	
Blood mercury, mean ± SD, µg/L	1.3 ± 0.06	1.4 ± 0.1	1.2 ± 0.1	**0.021**
Q1 (≤0.4)	1820 (27.0)	1694 (27.2)	126 (23.8)	0.219
Q2 (>0.4–0.8)	1875 (26.1)	1734 (26.2)	141 (25.1)	
Q3 (>0.8–1.6)	1663 (24.2)	1504 (23.9)	129 (28.8)	
Q4 (>1.6)	1776 (22.7)	1653 (22.8)	123 (22.3)	
Missing	2453	2260	193	
Urinary arsenic, mean ± SD, µg/g creatinine	16.6 ± 1.5	16.6 ± 1.6	17.7 ± 3.3	0.757
Q1 (≤3.7)	842 (29.3)	791 (29.6)	51 (24.5)	0.596
Q2 (>3.7–6.5)	790 (24.6)	736 (24.6)	54 (24.8)	
Q3 (>6.5–14.3)	820 (24.3)	769 (24.3)	51 (25.1)	
Q4 (>14.3)	826 (21.8)	759 (21.5)	67 (25.6)	
Missing	6279	5790	489	
Plasma selenium, µg/L	195.3 ± 0.9	195.7 ± 0.9	189.6 ± 2.0	**0.002**
Q1 (≤176.8)	1723 (22.1)	1551 (21.4)	172 (32.5)	**<0.001**
Q2 (>176.8–191.4)	1826 (25.5)	1714 (25.7)	112 (22.6)	
Q3 (>191.4–207.1)	1756 (25.7)	1642 (26.0)	114 (20.4)	
Q4 (>207.1)	1799 (26.7)	1678 (26.9)	121 (24.5)	
Missing	2453	2260	193	
Serum folate, ng/mL	19.3 ± 0.3	18.8 ± 0.3	26.4 ± 1.1	**<0.001**
Q1 (≤11.4)	2284 (25.2)	2144 (25.5)	140 (19.8)	**<0.001**
Q2 (>11.4–16.3)	2170 (23.7)	2058 (24.2)	112 (17.3)	
Q3 (>16.3–23.9)	2096 (25.1)	1967 (25.4)	129 (20.5)	
Q4 (>23.9)	2092 (26.0)	1844 (24.9)	248 (42.4)	
Missing	915	832	83	

Table 1. Blood and urine parameters, demographic characteristics, lifestyle and comorbid conditions of the study population with or without CKD. (Cont'd)

Variables	Overall[a] (n=9557)	CKD		*P* value
		No (n=8845)	Yes (n=712)	
RBC folate, ng/mL	409.0 ± 9.8	401.1 ± 9.7	530.0 ± 25.1	**<0.001**
Q1 (≤41.1)	2231 (24.9)	2101 (25.2)	130 (20.2)	**<0.001**
Q2 (>41.1–396.9)	2101 (22.3)	1991 (22.6)	110 (17.2)	
Q3 (>396.9–556.3)	2140 (25.0)	2004 (25.3)	136 (21.0)	
Q4 (>556.3)	2125 (27.8)	1879 (26.9)	246 (41.6)	
Missing	960	870	90	
Serum zinc, μg/dL	88.5 ± 0.5	88.7 ± 0.5	84.5 ± 1.8	**0.013**
Q1 (≤71.0)	229 (8.8)	195 (8.2)	34 (20.2)	**0.003**
Q2 (>71.0–80.4)	484 (19.0)	445 (18.9)	39 (20.8)	
Q3 (>80.4–90.3)	725 (32.0)	684 (32.3)	41 (26.6)	
Q4 (>90.3)	903 (40.2)	863 (40.6)	40 (32.4)	
Missing	7216	6658	558	
Age, years	46.7 ± 0.3	45.2 ± 0.3	68.5 ± 0.5	**<0.001**
18–29	1895 (21.0)	1890 (22.4)	5 (0.7)	
30–39	1516 (17.4)	1497 (18.3)	19 (3.8)	
40–59	3078 (35.1)	2995 (36.7)	83 (13.1)	
60–79	2533 (22.6)	2157 (20.3)	376 (55.4)	
80+	535 (3.9)	306 (2.3)	229 (27.0)	
Sex				
Male	4627 (48.5)	4316 (49.4)	311 (36.0)	**<0.001**
Female	4930 (51.5)	4529 (50.6)	401 (64.0)	
Race				
Non-Hispanic whites	3578 (64.4)	3170 (63.4)	408 (78.9)	**<0.001**
Non-Hispanic blacks	2007 (11.3)	1887 (11.6)	120 (8.1)	
Other Hispanic	1350 (8.9)	1297 (9.3)	53 (3.3)	
Others + Mexican American	2622 (15.3)	2491 (15.7)	131 (9.7)	
Poverty income ratio				
Not poor ≥1	6649 (84.1)	6118 (83.8)	531 (87.9)	**0.029**
Poor <1	2004 (15.9)	1886 (16.2)	118 (12.1)	
Missing	904	841	63	
Education level				
≤ High school	4021 (37.5)	3656 (37.1)	365 (43.5)	**0.029**
College or above	5086 (62.5)	4741 (62.9)	345 (56.5)	
Missing	450	448	2	
Vigorous physical activity	1909 (22.6)	1834 (23.4)	75 (11.9)	**<0.001**

Table 1. Blood and urine parameters, demographic characteristics, lifestyle and comorbid conditions of the study population with or without CKD. (Cont'd)

Variables	Overall[a] (n=9557)	CKD		*P* value
		No (n=8845)	Yes (n=712)	
BMI, category				
Underweight	284 (2.5)	262 (2.5)	22 (2.5)	**0.019**
Normal	2670 (27.8)	2518 (28.2)	152 (21.5)	
Overweight	3020 (32.0)	2782 (32.0)	238 (33.2)	
Obese	3583 (37.7)	3283 (37.3)	300 (42.7)	
Smoking status				
Never	5491 (57.0)	5137 (57.3)	354 (53.1)	**0.001**
Former	2196 (24.7)	1921 (23.8)	275 (37.2)	
Current smoker	1750 (18.3)	1667 (18.9)	83 (9.6)	
Missing	120	120	0	
Excessive alcohol consumption	426 (5.5)	396 (5.5)	30 (5.6)	0.952
Hypertension	3678 (34.7)	3130 (32.0)	548 (73.6)	**<0.001**
DM	1620 (12.5)	1355 (11.1)	265 (32.1)	**<0.001**
Hyperlipidaemia	5042 (52.0)	4515 (50.4)	527 (75.2)	**<0.001**
CVD history	1006 (9.0)	738 (7.2)	268 (34.8)	**<0.001**
COPD	659 (6.9)	566 (6.5)	93 (13.2)	**<0.001**

BMI: body mass index; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CVD: cardiovascular disease; DM: diabetes mellitus; Q: quartile

[a] The cohort size (n=9557) was equivalent to 236,263,413 weighted population in the US after applying the sample weights provided by NHANES.

Values in bold are statistically significant.

Unless indicated otherwise, all values in brackets are expressed in no. (%) of participants.

Industrial development, which intends to meet the demands of a growing and modern population, has contributed to extremely dangerous chemicals in the environment that broadly affect human health—including heavy metals. Several previous studies investigated whether metal exposure is associated with adverse effects on kidney injury biomarkers, kidney function or changes in blood pressure in children or adolescents.[23,24] Several studies have found significant associations between heavy metals and reductions in GFR, and provided meaningful underlying data on renal function and heavy metals.[11,12,25] Another study has pointed out that excessive cadmium excretion may indicate renal tubular damage, showing that heavy metals and their combinations may affect renal parameters.[12] The effects of low-level exposure to multiple metals on renal function in early life may have profound implications on developing hypertension, renal disease and renal insufficiency later in life.[11] Oxidative stress plays a crucial role in many diseases, including CKD. In vitro studies have identified arsenic- or cadmium-induced oxidative stress in rat kidney or renal tubular epithelial cells.[23] Mercury, arsenic, lead, cadmium and chromium are the most common heavy metals that can cause chronic or acute poisoning when inhaled or ingested via air, water and food. Different body tissues have different toxic effects on the bioaccumulation of heavy metals.[26] Heavy metals can damage cellular processes, including proliferation, growth, apoptosis, damage repair and differentiation. The pathways through which these metals induce toxicity are similar to damage manifestation, including reactive oxygen species production, weakened antioxidant defences, enzymatic inactivation and oxidative stress.

In this study, univariate analysis indicated that higher quartiles of blood lead and cadmium were associated with greater odds of CKD compared with the lowest quartile. However, as plasma selenium and serum zinc

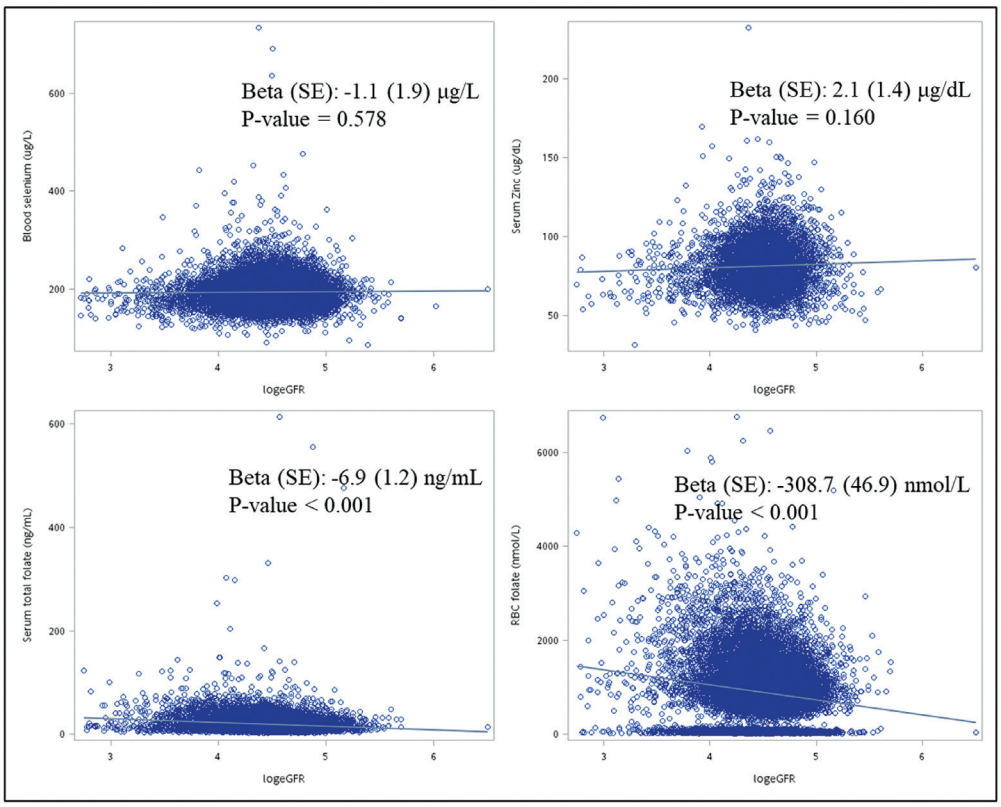

Fig. 2. Associations between $\log_{10}$ GFR, plasma selenium, zinc, serum folate and RBC folate.

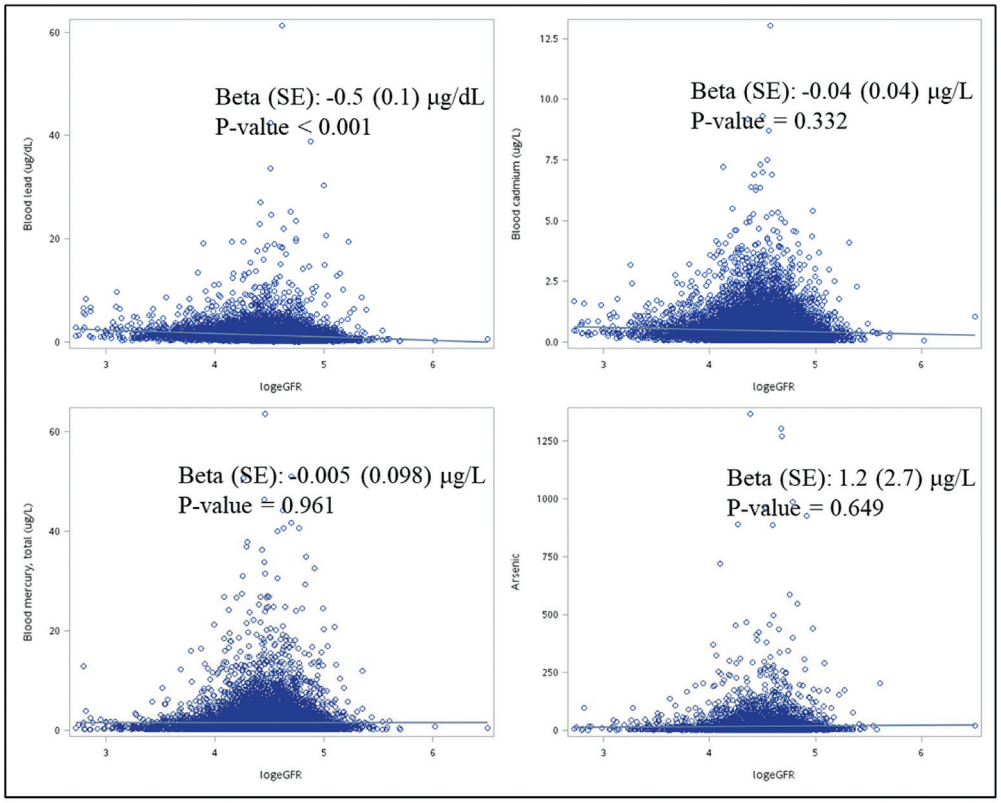

Fig. 3. Associations between $\log_{10}$ GFR, blood lead, cadmium, mercury and urine arsenic.

Table 2. Associations between study variables and prevalent CKD.

Variables		CKD	
	Number	Univariate (OR, 95% CI)	Multivariable (AOR, 95% CI)
Blood lead, μg/dL	7104		
Q1 (≤0.6)		ref	ref
Q2 (>0.6–1.0)		**1.84 (1.22–2.76)**	0.73 (0.43–1.24)
Q3 (>1.0–1.6)		**3.24 (2.14–4.89)**	1.01 (0.57–1.78)
Q4 (>1.6)		**4.20 (2.76–6.40)**	1.01 (0.58–1.77)
Blood cadmium, μg/L	7104		
Q1 (≤0.2)		ref	ref
Q2 (>0.2–0.3)		**2.47 (1.70–3.59)**	1.49 (0.94–2.35)
Q3 (>0.3–0.6)		**4.60 (3.34–6.32)**	**1.93 (1.25–3.00)**
Q4 (>0.6)		**3.23 (1.98–5.27)**	**2.79 (1.58–4.92)**
Blood mercury, μg/L	7104		
Q1 (≤0.4)		ref	ref
Q2 (>0.4–0.8)		1.09 (0.81–1.48)	0.84 (0.58–1.22)
Q3 (>0.8–1.6)		1.38 (1.00–1.90)	1.11 (0.75–1.63)
Q4 (>1.6)		1.12 (0.79–1.59)	0.77 (0.49–1.20)
Urine arsenic, μg/g creatinine	3278		
Q1 (≤3.7)		ref	ref
Q2 (>3.7–6.5)		1.22 (0.73–2.03)	1.13 (0.64–2.01)
Q3 (>6.5–14.3)		1.24 (0.71–2.17)	0.93 (0.47–1.87)
Q4 (>14.3)		1.43 (0.80–2.55)	0.74 (0.38–1.46)
Plasma selenium, μg/L	7104		
Q1 (≤176.8)		ref	ref
Q2 (>176.8–191.4)		**0.58 (0.40–0.84)**	**0.57 (0.36–0.90)**
Q3 (>191.4–207.1)		**0.51 (0.35–0.75)**	**0.58 (0.36–0.93)**
Q4 (>207.1)		**0.60 (0.43–0.83)**	**0.61 (0.40–0.92)**
Serum folate, ng/mL	8642		
Q1 (≤11.4)		ref	ref
Q2 (>11.4–16.3)		0.92 (0.63–1.34)	0.93 (0.60–1.44)
Q3 (>16.3–23.9)		1.04 (0.72–1.51)	0.81 (0.50–1.30)
Q4 (>23.9)		**2.20 (1.62–2.98)**	0.94 (0.64–1.38)
RBC folate, nmol/L	8597		
Q1 (≤41.1)		ref	ref
Q2 (>41.1–396.9)		0.95 (0.69–1.32)	1.11 (0.73–1.70)
Q3 (>396.9–556.3)		1.04 (0.75–1.44)	1.11 (0.70–1.74)
Q4 (>556.3)		**1.94 (1.49–2.52)**	1.27 (0.86–1.87)
Serum zinc, μg/dL	2341		
Q1 (≤71.0)		ref	ref
Q2 (>71.0–80.4)		**0.44 (0.23–0.86)**	**0.39 (0.18–0.87)**
Q3 (>80.4–90.3)		**0.33 (0.19–0.60)**	**0.32 (0.15–0.71)**
Q4 (>90.3)		**0.32 (0.16–0.66)**	**0.30 (0.13–0.69)**

Multivariable models were adjusted for age (continuous), gender, race, poverty-to-income ratio, education level, vigorous physical activity, body mass index (BMI), smoking status, hypertension, diabetes mellitus (DM), hyperlipidaemia, cardiovascular disease (CVD) and chronic obstructive pulmonary disease (COPD).

Table 3. Combined effects of selenium or zinc with blood lead, cadmium, mercury, urine arsenic on CKD.

Variables	CKD		
	Number	Univariate (OR, 95% CI)	Multivariable (AOR, 95% CI)
Selenium x Lead	1774		
Low Selenium x high Lead		ref	ref
Low Selenium x low Lead		**0.13 (0.06–0.29)**	0.73 (0.24–2.24)
High Selenium x high Lead		0.73 (0.44–1.21)	0.96 (0.44–2.11)
High Selenium x low Lead		**0.14 (0.06–0.35)**	0.48 (0.15–1.53)
Selenium x Cadmium	1864		
Low Selenium x high Cadmium		ref	ref
Low Selenium x low Cadmium		**0.31 (0.14–0.68)**	0.62 (0.27–1.41)
High Selenium x high Cadmium		**0.14 (0.05–0.40)**	0.92 (0.50–1.69)
High Selenium x low Cadmium		0.87 (0.51–1.49)	**0.23 (0.07–0.72)**
Selenium x Mercury	1790		
Low Selenium x high Mercury		ref	ref
Low Selenium x low Mercury		1.03 (0.51–2.08)	1.04 (0.46–2.35)
High Selenium x high Mercury		0.80 (0.40–1.60)	0.69 (0.23–2.69)
High Selenium x low Mercury		0.68 (0.32–1.45)	1.02 (0.39–2.69)
Selenium x Arsenic	835		
Low Selenium x high Arsenic		ref	ref
Low Selenium x low Arsenic		0.87 (0.31–2.42)	1.22 (0.41–3.58)
High Selenium x high Arsenic		0.59 (0.21–1.62)	0.32 (0.06–1.66)
High Selenium x low Arsenic		**0.20 (0.07–0.56)**	0.38 (0.09–1.66)
Zinc x Lead	517		
Low Zinc x high Lead		ref	ref
Low Zinc x low Lead		**0.11 (0.02–0.72)**	0.50 (0.05–5.02)
High Zinc x high Lead		**0.18 (0.06–0.54)**	**0.10 (0.03–0.33)**
High Zinc x low Lead		**0.04 (0.01–0.31)**	**0.08 (0.01–0.65)**
Zinc x Cadmium	617		
Low Zinc x high Cadmium		ref	ref
Low Zinc x low Cadmium		0.26 (0.04–1.63)	0.75 (0.08–7.15)
High Zinc x high Cadmium		**0.19 (0.04–0.80)**	**0.10 (0.02–0.43)**
High Zinc x low Cadmium		**0.08 (0.01–0.45)**	**0.11 (0.02–0.76)**
Zinc x Mercury	560		
Low Zinc x high Mercury		ref	ref
Low Zinc x low Mercury		0.33 (0.10–1.13)	0.36 (0.05–2.37)
High Zinc x high Mercury		**0.15 (0.04–0.51)**	**0.15 (0.02–0.97)**
High Zinc x low Mercury		**0.16 (0.05–0.59)**	**0.09 (0.02–0.58)**
Zinc x Arsenic	535		
Low Zinc x high Arsenic		ref	ref
Low Zinc x low Arsenic		0.35 (0.10–1.29)	0.21 (0.02–2.76)
High Zinc x high Arsenic		**0.10 (0.03–0.35)**	**0.01 (<0.001–0.13)**
High Zinc x low Arsenic		**0.13 (0.04–0.43)**	**0.07 (0.01–0.65)**

Multivariable models were adjusted for age (continuous), gender, race, poverty-to-income ratio, education level, vigorous physical activity, body mass index (BMI), smoking status, hypertension, diabetes mellitus (DM), hyperlipidaemia, cardiovascular disease (CVD) and chronic obstructive pulmonary disease (COPD).

increased, the odds of CKD decreased. These results were upheld in multivariate analysis after adjusting for relevant confounders. Statistically significant associations were found between higher quartiles of plasma selenium and serum zinc and lower odds of CKD, similar to results found in previous studies. One previous study indicated that adequate selenium consumption may have a positive effect on the treatment and prevention of CKD.[27] Another study reported an association between blood cadmium and blood lead levels and adverse renal outcomes.[28] Decreased glomerular filtration results in increasing the accumulation of cadmium and lead in the blood, and decreased urinary excretion of cadmium and lead. Patients with lower eGFR may retain these heavy metals, exacerbating their toxic effects on the other organs and kidneys. Another study investigating CKD using a large-scale health programme in Taiwan found that drinking water containing high arsenic concentrations is a risk factor for the rapid progression of CKD.[29]

Selenium is an antioxidant nutrient that plays a vital role in biological defence against oxidative damage.[24] A previous study suggested that selenium can alter eGFR in environmental toxicant-induced CKD, and highlighted the need for nutrition and environmental modifications to improve kidney health.[30] Another study revealed that selenium functions by forming selenoproteins that contribute to antioxidant defence, immune response and thyroid hormone production in various biological processes.[31] Selenium plays a crucial role in reducing the toxicity of arsenic, lead, mercury and cadmium.

Zinc is an essential metal in many physiological functions, including immune maturation, reproduction and cell growth.[17] It is also an essential component of copper and zinc superoxide dismutase, acts as a protector for thiols and other chemical groups, and provides protection against free radical damage by maintaining sufficient metallothionein levels.[32] In many important enzymatic reactions, zinc acts as a vital cofactor, such as for liver alcohol dehydrogenase, carbonic anhydrase and carboxypeptidase. A previous study suggested that low dietary zinc consumption may increase the risk of CKD in individuals with normal renal function.[33] Zinc has similar physical and chemical properties to cadmium and can compete for binding sites in metal-absorbing proteins and enzyme proteins.

Limitations

Our study was cross-sectional and retrospective, and inferences of causality could not be made confidently regarding the observed associations. Reverse causality might have operated, e.g. patients with milder CKD had higher intakes of selenium and zinc, or their proximal convoluted tubules retained more selenium and zinc, or both, than the patients with severe CKD. Results also might not be generalisable to other populations aside from those within NHANES. Measurements were collected at only one time point, so the cross-sectional nature of the study did not allow for a longitudinal assessment of GFR over at least 3 months. Moreover, the single-point measurements of nephrotoxic metals do not fully reflect each participant's real cumulative exposure levels. In NHANES, urine and blood sample collection times were not standardised, which does not support the complete accuracy of metal and micronutrient levels that may fluctuate over time.[34] Despite controlling for covariates, residual and unmeasured confounders and errors in measurement might still have biased the results.

CONCLUSION

The likelihood of CKD is increased in individuals with elevated levels of toxic heavy metals in the blood but is decreased with elevated levels of plasma selenium and serum zinc. High serum zinc appears to interact with low-toxicity heavy metals to reduce the risk of developing CKD. The results suggest that increased blood concentrations of selenium or zinc, or both, along with avoidance of heavy metal exposures, could protect against CKD.

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ORIGINAL ARTICLE

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Poorer outcomes following COVID-19 infection for patients with depression: A cohort analysis in South Korea

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ABSTRACT

Introduction: It remains unknown whether patients with pre-existing depressive conditions are at high risk of severe COVID-19. Therefore, this study aims to investigate the association between patients with pre-existing depressive conditions and severe COVID-19.

Method: This study is part of the Korea Disease Control and Prevention Agency-COVID19-National Health Insurance Service cohort study of an ongoing large-scale health screening survey of adults 18 years and older residing in South Korea. Pre-existing depression status was measured from 552,860 patients who participated in a biennial health screening from 2019 to 2020. Finally, 29,106 confirmed COVID-19 patients were enrolled and followed up to track any severe clinical events within 1 month of their diagnosis date. Adjusted odds ratio (aOR) and 95% confidence interval (CI) were calculated using multivariate-adjusted logistic regression analysis.

Results: We identified 2868 COVID-19 patients with severe clinical events and 26,238 COVID-19 patients without severe clinical events. The moderate-to-severe depressive symptoms group showed an elevated odds of severe outcomes of COVID-19 (aOR, 1.46; 95% CI, 1.25–1.72), including those without vaccination (aOR, 1.32; 95% CI, 1.08–1.61) and those with complete vaccination (aOR, 1.76; 95% CI, 1.18–2.63). In addition, those who were diagnosed with depression along with depressive symptoms at the health screening revealed an increased risk of severe outcomes of COVID-19 (aOR, 2.22; 95% CI, 1.22–4.05).

Conclusion: Moderate-to-severe depressive symptoms were associated with higher odds of severe COVID-19 events in both no and complete vaccination groups. Participants with depressive symptoms may be at higher risk of severe outcomes of COVID-19.

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Keywords: cohort study, pre-existing depression, public mental health, severe COVID-19, social science, South Korea

INTRODUCTION

In the early days of the pandemic, a major public health focus was to slow the spread of COVID-19. Therefore, the emphasis was on protecting the elderly, immunocompromised, and patients with respiratory and other underlying medical conditions. However, as COVID-19 continues to prolong, the concept of a new "normal" has emerged and is moving in a direction that focuses more on health risks to other vulnerable population groups, including individuals with severe mental illness.[1]

The COVID-19 pandemic disproportionately affects people with pre-existing mental health disorders.[2] They are a vulnerable group in consideration of both medical and socioeconomic aspects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, morbidity and mortality.[3] This increased risk is likely to be mediated by the risk factors for infectious diseases, including socioeconomic inequality, poverty, unemployment, social distancing, and physical inactivity.[4]

There is evidence that pre-existing health inequalities may be strongly reflected in the current COVID-19

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CLINICAL IMPACT

What is New

- To the authors' knowledge, this cohort study is one of the first to highlight the epidemiological need to screen a vulnerable group in Korea with pre-existing depressive symptoms.

Clinical Implications

- This study supports the need to increase awareness of severe COVID-19 vulnerable groups and preventive management of people with moderate-to-severe depression.
- Our results could aid mental public health policymaking and guide efforts to improve preventive strategies against the risk of communicable diseases.

pandemic.[5] Patients with pre-existing mental disorders are at increased risk of contracting COVID-19 and are particularly vulnerable to the mental health threat of the pandemic.[6-8] Some longitudinal evidence suggests that the type of pre-existing mental health condition predicts different levels or changes in depressive and anxiety symptoms during a pandemic.[9] However, studies on the health risk effects according to pre-COVID-19 depressive symptoms or mental health conditions remain limited.

In the meantime, there have been previous studies on the risk that mental illness, such as severe depression, increases the risk of SARS-CoV-2 infection[10] and subsequent severe COVID-19.[11] However, it is still unclear how the epidemic and the prevalence of depression may affect SARS-CoV-2 infection, severe COVID-19, and mortality. Most previous studies were cross-sectional, targeting specific population groups affected by the COVID-19 pandemic, such as mental health service providers and their stakeholders[2] or people self-reporting a mood disorder,[12] who demonstrated the results of the primary survey. A few studies have explored the long-term effects of pre-existing depression on SARS-CoV-2 infection and severe COVID-19 in a large-scale population-based cohort. In the present study, we evaluated the association of pre-existing depressive status and severe clinical outcomes of COVID-19 in the Korea Disease Control and Prevention Agency-COVID19-National Health Insurance Service (K-COV-N) cohort, which represents up to 97% of all Korean citizens.[13]

METHOD

Data source

The current cohort study used data from the K-COV-N cohort. The National Health Insurance Service (NHIS) provides health insurance services to approximately 97% of the Korean population.[13] Health insurance claims—including medical health screening results, medical treatments, and medication prescriptions—have been collected by the NHIS. The Korea Disease Control and Prevention Agency (KDCA) operated as the Central Disease Control Headquarters for COVID-19 and collected data on COVID-19 and vaccinations. To promote academic research in analysing health damage caused by COVID-19 and to actively develop treatments for preventing infectious diseases, the NHIS and KDCA have linked the national health information with COVID-19-related records and thereby generated the K-COV-N cohort dataset. The eligibility dataset contains (1) demographic data, medical history, anthropometric measurements, and lifestyle questionnaires from the NHIS registered between 1 January 2009 and 31 December 2021; and (2) date of confirmation of COVID-19, date of death, area code of reporting institution, mode of transmission, dose of COVID-19 vaccines administered with the vaccination date, and type from the KDCA registered between 8 October 2020 and 31 December 2021. The dataset was matched by a confirmed COVID-19 case population with a 1:10 ratio using age and sex propensity scores. The COVID-19-related registers after 8 October 2020 were used due to the possibility of identifiability even though the personally identifiable data were strictly anonymised. Access to the dataset was allowed only after approval by the enquiry committee.

Study population

A total of 2,882,789 participants who participated in health screenings from 2019 to 2020 were initially enrolled in the study. Among the participants who joined the health screenings, we excluded those who were not included for Patient Health Questionnaire-9 (PHQ-9) (n=2,329,929), diagnosed with COVID-19 before the follow-up period (n=17,228), and with missing information for other covariates (n=600). To investigate the association between the degree of depression severity and severe clinical events of COVID-19, we only included patients diagnosed with COVID-19 (n=44,706). A positive laboratory result by real-time RT-PCR assay was considered a confirmed case. Those who died within 1 month after COVID-19 infection before the severe clinical events (n=167) or were diagnosed with SARS-CoV-2 infection after

1 December 2021 due to a short follow-up period (n=15,433) were additionally excluded. Finally, 29,106 confirmed COVID-19 patients were enrolled and followed up from the diagnosis date to any severe clinical events within 1 month (Fig. 1). The Institutional Review Board of CHA University Hospital approved the study (No.: CHAMC 2022-05-052), and informed consent was waived due to anonymous cohort data provided by the NHIS and KDCA.

Exposure

The degree of depression severity was measured by PHQ-9. PHQ-9 is the most commonly used self-reported questionnaire formed with nine questions for screening depression in primary care.[3] The NHIS provides PHQ-9 to those aged 20, 30, 40, 50, 60 and 70 at the check-up year for screening depression. Participants were asked to answer each item by a score ranging from 0–3 (0=not at all; 1=several days; 2=more than half the days; 3=nearly every day). Then, we summed each score in total and categorised it into 3 levels: no depressive symptoms (scores of 0–4), mild depressive symptoms (scores of 5–9), and moderate-to-severe depressive symptoms (scores of 10–27). The accuracy of PHQ-9 in detecting depression[4-5] and its severity[6] has been validated through previous studies. The items in PHQ-9 are described elsewhere.[7]

Outcome

Outcome was defined as any severe event that occurred within one month after the diagnosed date, including the requirement of oxygen supply with conventional oxygen therapy (COT), a high-flow nasal cannula, continuous positive airway pressure, admission to intensive care unit, the requirement of mechanical ventilation, extracorporeal membrane oxygenation, and death after severe clinical events of COVID-19. When the total number for each outcome was lower than 5, it was not described in the table.

We also categorised the study population by vaccination status to reduce bias. Vaccination status was classified by the completion of the primary series of any COVID-19 vaccines. The COVID-19 vaccines available in South Korea include BNT162b2 (Pfizer-

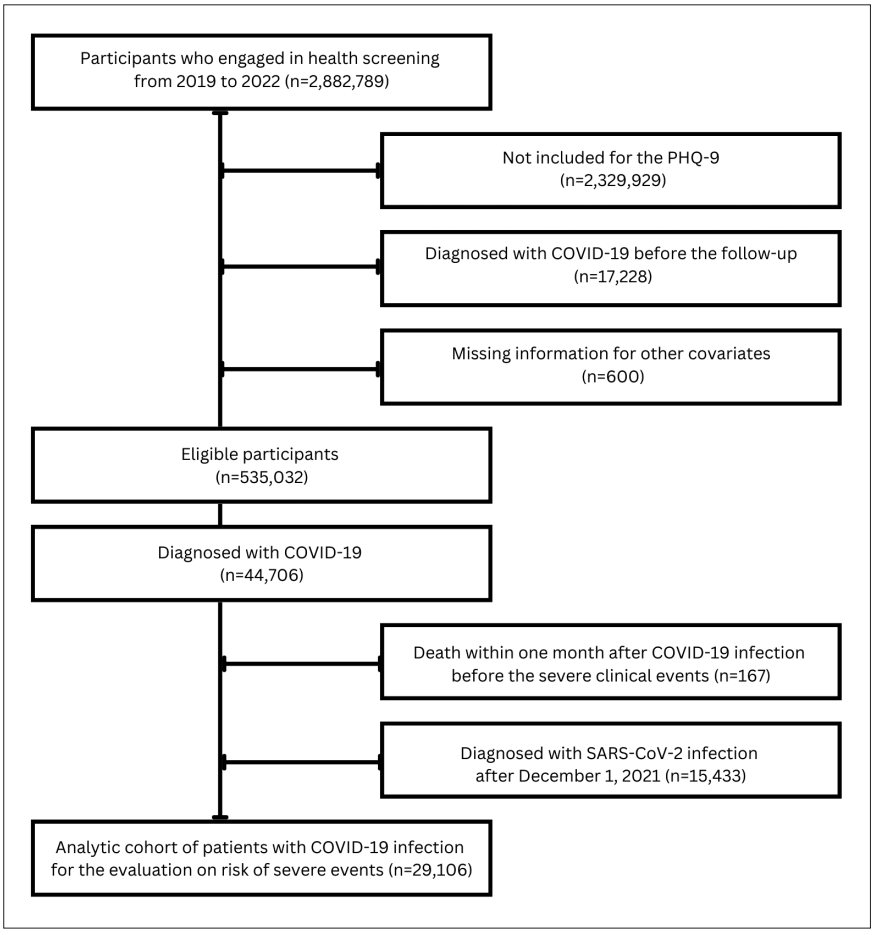

Fig. 1. Participant inclusion flowchart.

BioNTech), mRNA-1273 (Moderna), ChAdOx1 nCoV-19 (AstraZeneca), NVX-CoV2373 (Novavax), and Ad26.COV2.S (Janssen/Johnson & Johnson) vaccines. We considered those with any heterologous COVID-19 vaccines as completion of the primary series if the number of doses was 2 or more. If the patient was diagnosed with COVID-19 within 14 days after vaccination, we did not count them as vaccinated due to the relatively short period for vaccine effectiveness.

Covariates

For the adjustment, covariates were identified from the patient information before the start of follow-up. We included age, sex, household income, body mass index (BMI), smoking, alcohol consumption, moderate-to-vigorous physical activity (MVPA), history of hypertension, diabetes mellitus, dyslipidaemia, autoimmune disorder, history of organ transplantation, and comorbidities. Household income was categorised as quartiles based on the insurance premium. Smoking was categorised as ever or never smoker, differentiating patients between those that smoked or did not smoke at least 100 cigarettes throughout their lifetime, respectively. Alcohol consumption was categorised by the current alcohol intake as drinker or non-drinker. MVPA was assessed by the duration of weekly MVPA using self-reported questionnaires. By multiplying the times per day (minutes per day) with the frequency per week (days per week) for moderate and vigorous physical activity, we categorised it into 4 levels: physically inactive; 1–74 min/week; 75–149 min/week; and ≥150 min/week. Underlying comorbidities were assessed by Charlson Comorbidity Index (CCI) score using claims data before the follow-up validated in the previous study.[14] Diagnosis of hypertension, diabetes mellitus, and dyslipidaemia was confirmed by the records of medical diagnosis from clinical physicians collected at the health screening. The history of organ transplantation was based on the Electronic Data Interchange codes of kidney, liver, heart, lung, pancreas, bone marrow, and small intestine during hospitalisation (Table S1). The history of autoimmune disorders was confirmed based on the ICD-10 codes from a previous study (Table S2).

Statistical analysis

We analysed the association of the degree of depression severity with the odds of severe clinical COVID-19 events. From the diagnosis date of COVID-19, the patients were followed up for one month for any severe COVID-19 events. Continuous variables were presented as mean ± standard deviation (SD) and categorical variables as n (%). Event numbers for the outcomes were presented as n (%). Adjusted odds ratio (aOR) and 95% confidence interval (CI) were calculated using multivariate logistic regression analysis. First, age and sex were adjusted for the multivariate regression. Next, covariates including age, sex, household income, BMI, smoking, alcohol consumption, MVPA, history of hypertension, diabetes mellitus, dyslipidaemia, and CCI were adjusted. To reduce healthy vaccine bias, we categorised the patients by vaccination status depending on the completion of the primary series. To validate the degree of depression severity, we correlated every patient with the diagnosis of depression (ICD-10 codes of F32-F33) after the health screening. Individuals indicating an absence of depressive symptoms and without a diagnosis of depression were categorised as "devoid of depressive symptoms — authentic absence". Similarly, those who reported moderate-to-severe depressive symptoms and were diagnosed with depression were considered as "moderate-to-severe depressive — genuine depression". For the subgroup analyses, we stratified the patients with age (<65, ≥65), sex (men, women), comorbidity (CCI; 0, 1, ≥2), hypertension (yes, no), diabetes mellitus (yes, no), and dyslipidaemia (yes, no) with the risk of severe COVID-19. *P* values of less than 0.05 were considered statistically significant in a two-sided manner. All data collection, mining, and statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

The analytic cohort consisted of 29,106 adults aged 20 or more years who engaged in health screening from 2019 to 2020. Among them, 23,027 showed no depressive symptoms, 4404 showed mild depressive symptoms, and 1675 showed moderate-to-severe depressive symptoms. Compared with no depressive symptoms, those with moderate-to-severe depressive symptoms tended to be younger, women, physically inactive, have lower household income, have lower systolic blood pressure, have lower diastolic blood pressure, have lower CCI, and have no COVID-19 vaccination. Other descriptive characteristics are described in Table 1.

Association of depression severity with the risk of severe COVID-19

There were 3,023 severe clinical COVID-19 events that occurred during the follow-up period. Table 2 shows the associations between depression severity with the risk of severe clinical COVID-19 events and stratified

Table 1. Descriptive characteristics of the study participants.

	No depressive symptoms (n=23,027)	Mild depressive symptoms (n=4404)	Moderate-to-severe depressive symptoms (n=1675)
Age, years	49.2 ± 13.9	44.8 ± 13.5	44.3 ± 14.1
Sex, n (%)			
Men	11,903 (51.7)	1914 (43.5)	633 (37.8)
Women	11,124 (48.3)	2490 (56.5)	1042 (62.2)
Moderate-to-vigorous physical activity, n (%)			
Physically inactive	6172 (26.8)	1353 (30.7)	574 (34.3)
1–74 min/week	5008 (21.8)	1103 (25.1)	345 (20.6)
75–149 min/week	2966 (12.9)	612 (13.9)	217 (13.0)
≥150 min/week	8881 (38.6)	1336 (30.3)	539 (32.2)
Household income, n (%)			
First quartile	5073 (22.0)	953 (21.6)	437 (26.1)
Second quartile	5023 (21.8)	996 (22.6)	405 (24.2)
Third quartile	6057 (26.3)	1237 (28.1)	432 (25.8)
Fourth quartile (highest)	6874 (29.9)	1218 (27.7)	401 (23.9)
Body mass index, kg/m2	24.6 ± 3.6	24.5 ± 4.0	24.4 ± 4.1
Waist circumference, cm	82.6 ± 10.2	81.8 ± 17.8	81.4 ± 11.0
Systolic blood pressure, mmHg	122.2 ± 14.8	121.7 ± 14.4	121.1 ± 14.1
Diastolic blood pressure, mmHg	77.0 ± 10.4	75.8 ± 10.6	75.9 ± 10.3
Triglyceride, mg/dL	133.5 ± 108.5	136.7 ± 123.7	146.0 ± 126.8
Cigarette smoking, n (%)			
Never smoker	15,049 (51.7)	2805 (63.7)	1016 (60.7)
Ever smoker	7978 (34.7)	1599 (36.3)	659 (39.3)
Alcohol consumption, n (%)			
Yes	15,044 (65.3)	3263 (74.1)	1217 (72.7)
No	7983 (34.7)	1141 (25.9)	458 (27.3)
Hypertension, n (%)	4232 (18.4)	636 (14.4)	257 (15.3)
Diabetes, n (%)	1744 (7.6)	283 (6.4)	123 (7.3)
Dyslipidaemia, n (%)	1747 (7.6)	313 (7.1)	144 (8.6)
Organ transplantation, n (%)	6 (0.0)	1 (0.0)	0 (0.0)
Autoimmune disease, n (%)	3747 (16.3)	785 (17.8)	378 (22.6)
Charlson comorbidity index, n (%)			
0	9495 (41.2)	1837 (41.7)	604 (36.1)
1	7828 (34.0)	1490 (33.8)	573 (34.2)
≥2	5704 (24.8)	1077 (24.5)	498 (29.7)
COVID-19 vaccination, n (%)			
No	12,799 (55.6)	2713 (61.6)	1040 (62.1)
Completion of primary series	6436 (28.0)	1020 (23.2)	363 (21.7)

Continuous variables were presented as mean ± standard deviation and categorical variables as n (%). Degree of depression severity was measured by PHQ-9 at the NHIS health screening test from 2019 to 2020. By adding the scores of each 9 items, total score was calculated and categorised by 3 levels: no depressive symptoms (scores of 0–4), mild depressive symptoms (scores of 5–9), moderate-to-severe depressive symptoms (scores of 10–27).
Acronyms: COVID-19, coronavirus disease 2019; PHQ-9, Patient Health Questionnaire-9; NHIS, National Health Insurance Service.

the results with the vaccination status. Compared with those who showed no depressive symptoms, the moderate-to-severe depressive symptoms group showed an elevated risk (aOR, 1.46; 95% CI, 1.25–1.72). The risk was consistent when stratified with no vaccination (aOR, 1.33; 95% CI, 1.09–1.62) and completion of the primary series (aOR, 1.65; 95% CI, 1.11–2.47). There were 22,644 authentic absence and 160 genuine depression patients when correlated with the diagnosis of depression after testing for PHQ-9 (Table S3). When validated with the diagnosis of depression after the health screening test, the odds increased (aOR, 1.99; 95% CI, 1.12–3.53, Table 3). However, the odds showed no significance when stratified with the vaccination status. Those who were treated for COT showed statistically significant results when moderate-to-severe depressive symptoms were exhibited (aOR, 1.48; 95% CI, 1.26–1.74, Table S4). The risk was consistent for COT when moderate-to-severe depressive symptoms were shown, stratified with no vaccination (aOR, 1.34; 95% CI, 1.10–1.63, Table S5) and completion of the primary series (aOR, 1.76; 95% CI, 1.19–2.65, Table S6). Other outcomes showed no significant results.

Stratified analysis

A stratified analysis of the association of depression severity with the risk of severe clinical COVID-19 events is shown in Table S7. All patients were stratified by age, sex, hypertension, diabetes mellitus, dyslipidaemia, and CCI. Those with age <65 years (aOR, 1.34; 95% CI, 1.12–1.59), women (aOR, 1.55; 95% CI, 1.26–1.93), and history of dyslipidaemia (aOR, 1.81; 95% CI, 1.13–2.98) had an elevated risk when they had moderate-to-severe depressive symptoms. Conversely, the risk was also elevated with no comorbidities (aOR, 1.66; 95% CI, 1.21–2.28), no

Table 2. Association of depression severity with the risk of severe clinical COVID-19 events.

Depressive symptoms[a]	Event	Age, sex-adjusted OR (95% CI)	Multivariable-adjusted OR (95% CI)[b]
Overall, 29106 (100%)			
No	2282 (7.8)	1.00 (Reference)	1.00 (Reference)
Mild	390 (1.3)	1.10 (0.98–1.23)	1.08 (0.96–1.21)
Moderate to severe	196 (0.7)	1.53 (1.31–1.80)[e]	1.46 (1.25–1.72)[e]
P for trend		<.001	<.001
No vaccination, 16552 (56.9%)			
No	1620 (9.8)	1.00 (Reference)	1.00 (Reference)
Mild	293 (1.8)	1.06 (0.93–1.22)	1.05 (0.92–1.21)
Moderate to severe	137 (0.8)	1.38 (1.14–1.68)[d]	1.33 (1.09–1.62)[d]
P for trend		0.004	0.02
Completion of primary series, 7819 (26.9%)			
No	382 (4.9)	1.00 (Reference)	1.00 (Reference)
Mild	54 (0.7)	1.15 (0.85–1.56)	1.13 (0.84–1.45)
Moderate to severe	32 (0.4)	1.89 (1.28–2.81)[d]	1.65 (1.11–2.47)[c]
P for trend		0.006	0.04

The patients were categorised by vaccination status depending on the completion of the primary series. aOR was calculated using multivariate adjusted logistic regression and presented with 95% CI. Event number of severe COVID-19 was presented as n (%). [a]Degree of depression severity was measured by PHQ-9 at the NHIS health screening test from 2019 to 2020. By adding the scores of each 9 items, total score was calculated and categorised by 3 levels: no depressive symptoms (scores of 0–4), mild depressive symptoms (scores of 5–9), moderate-to-severe depressive symptoms (scores of 10–27).
[b]Adjusted for age, sex, household income, body mass index (BMI), smoking, alcohol consumption, MVPA, history of hypertension, diabetes mellitus, dyslipidaemia, autoimmune disorder, history of organ transplantation, and Charlson comorbidity index.
[c]$P<0.05$.
[d]$P<0.01$.
[e]$P<0.001$.
Acronyms: MVPA, moderate-to-vigorous physical activity; COVID-19, coronavirus disease 2019; OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio.

Table 3. Association of depression severity with the risk of severe clinical COVID-19 events correlated with the diagnosis of depression.

Depressive symptoms – diagnosis[a]	Event	Multivariable-adjusted OR (95% CI)[b]
Overall		
Devoid of depressive symptoms — authentic absence	2226 (9.8)	1.00 (Reference)
Moderate-to-severe depressive — genuine depression	24 (0.1)	1.99 (1.12–3.53)[c]
P for trend		0.009
No vaccination		
Devoid of depressive symptoms — authentic absence	1578 (12.4)	1.00 (Reference)
Moderate-to-severe depressive — genuine depression	17 (0.1)	1.82 (0.85–3.93)
P for trend		0.13
Completion of primary series		
Devoid of depressive symptoms — authentic absence	372 (4.9)	1.00 (Reference)
Moderate-to-severe depressive — genuine depression	2 (0.0)	1.23 (0.15–9.95)
P for trend		0.85

The patients were categorised by vaccination status depending on the completion of the primary series. aOR was calculated using multivariate adjusted logistic regression and presented with 95% CI. Event number of severe COVID-19 was presented as n (%). [a]Degree of depression severity was measured by PHQ-9 at the NHIS health screening test from 2019 to 2020. By adding the scores of each 9 items, total score was calculated and categorised by 3 levels: no depressive symptoms (scores of 0–4), mild depressive symptoms (scores of 5–9), moderate-to-severe depressive symptoms (scores of 10–27). Every patient was correlated with the diagnosis of depression (ICD-10 code of F32–F33) after the health screening. Those who reported no depressive symptoms and were not diagnosed with depression were considered as devoid of depressive symptoms — authentic absence. Similarly, those who reported moderate-to-severe depressive symptoms and were diagnosed with depression were considered as moderate-to-severe depressive — genuine depression.
[b]Adjusted for age, sex, household income, body mass index (BMI), smoking, alcohol consumption, MVPA, history of hypertension, diabetes mellitus, dyslipidaemia, autoimmune disorder, history of organ transplantation, and Charlson comorbidity index.
[c]$P<0.05$.
[d]$P<0.01$.
[e]$P<0.001$.
Acronyms: MVPA, moderate-to-vigorous physical activity; COVID-19, coronavirus disease 2019; OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio; International Classification of Diseases, 10th Revision, ICD-10.

hypertension (aOR, 1.58; 95% CI, 1.32–1.90), diabetes mellitus (aOR, 1.50; 95% CI, 1.26–1.79), and no dyslipidaemia (aOR, 1.43; 95% CI, 1.20–1.70). No significant interaction was found between subgroups.

DISCUSSION

Pre-existing depressive status prior to the pandemic was associated with a higher odds of severe clinical COVID-19 events. Participants with moderate-to-severe depressive symptoms had a higher risk of severe COVID-19 events than those without pre-existing depressive symptoms. The results were consistent when stratified by the presence of vaccinations. In addition, moderate-to-severe depressive symptoms and diagnosis of depression had an over 2-fold risk of severe clinical events in patients with COVID-19. Further research is needed to determine whether depressive symptoms and depression may affect the long-term prognosis of COVID-19.

In previous studies, there was a bidirectional relationship between SARS-CoV-2 infection and mental health disorders. First, there were papers reporting the prevalence of depression,[15-16] anxiety,[17] or insomnia during the corona epidemic,[18] or exacerbating existing mental disorders.[17,19-20] Meanwhile, there have been studies reporting that patients with pre-existing general or severe mental health disorders have a higher risk of COVID-19,[7-8] severe consequences of COVID-19, and mortality.[10,19] That is, due to several socioeconomic factors, the COVID-19 pandemic disproportionately affects people with pre-existing mental health disorders,[10] including depression, anxiety, and psychotic disorders. To date, several countries have characterised the mental health status of the general population with respect to COVID-19, but there is a lack of efforts evaluating pre-existing depressive conditions against severe COVID-19 in a large-scale population that involved individuals without severe depressive conditions or disabilities.[12]

There are several possible reasons that could explain the association between depressive symptoms and severe COVID-19. One possible mechanism includes the

immune system's vulnerability caused by the depressed mood state,[25] making individuals more susceptible to infections like COVID-19.[26] Similarly, there may be a connection between the occurrence of inflammatory diseases and the depressive symptoms, indicating that the increased cytokines may have an impact on the mood state.[26] Depression is often accompanied by comorbidities such as obesity, diabetes and cardiovascular disease, which are known risk factors for severe COVID-19.[12] Another possible explanation is that the stress may lead to dysregulation of the hypothalamic-pituitary-adrenal axis, resulting in increased inflammation and oxidative stress, both of which may facilitate the pathogenesis of severe COVID-19.[27] Our study is consistent with the results of a population-based cohort study in Catalonia, which revealed that pre-existing mental health disorders were associated with the severity of COVID-19.[11] Our analysis of the NHIS cohort expands the evidence supporting the association between pre-COVID depression symptoms and the heightened risk of severe COVID-19, utilising large population-level data.

Our study differs from previous studies in that ours is based on claims data from the NHIS that routinely collects data on clinical and socioeconomic characteristics, including lifestyle habits, such as smoking, drinking, physical activity, household income and comorbidities, which allowed the comprehensive and robust adjustments of potential confounding factors. The limitations of our study include the unavailability of repeated measurements on depressive status before and after COVID-19 because the Korea NHIS provides mandatory healthcare services and health screening examinations biennially. Another concern is the short duration of follow-up that limited the assessment of long-term outcomes of COVID-19. It highlights the need for further longitudinal studies to determine the long-term impact of mental health prior to the pandemic against COVID-19. Lastly, the limited number of patients with severe COVID-19 patients may be a weakness. Despite the above limitations, this study presents the first robust association of pre-existing depressive symptoms with severe clinical COVID-19 events.

Taken together, patients with moderate-to-severe depressive symptoms had higher odds of severe clinical COVID-19 events. It may be necessary to additionally consider individuals with severe mental illness as a vulnerable population against severe clinical COVID-19 events.

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Competing interests

The authors declare that they have no competing interests.

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ORIGINAL ARTICLE

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Fetal congenital heart diseases: Diagnosis by anatomical scans, echocardiography and genetic tests

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ABSTRACT

Objective: To determine the distribution of major fetal congenital heart diseases (CHDs) diagnosed antenatally during routine second-trimester obstetric anatomical scans in an unselected population at a single tertiary centre and to characterise and stratify risk factors, genetic diagnosis and long-term health at 4 years old.

Method: A single-centre cohort study of all major fetal CHDs detected on routine obstetric fetal anatomical ultrasound scans between January 2014 and December 2017 was performed in an unselected population. Demographic details, fetal echocardiogram reports, genetic test results, delivery outcomes and postnatal progress were stratified by CHD subtype.

Results: Of 20,031 screened pregnancies, 109 pregnancies (0.53%) had major fetal CHDs. The most common subtypes were coarctation of aorta (17.4%), transposition of great arteries (16.5%), and tetralogy of Fallot and univentricular hearts (13.8% each). Of the 60.5% that underwent confirmatory genetic testing—mostly conventional karyotyping and testing for 22q11 microdeletion—about a quarter had abnormalities, of which 22q microdeletion was the most common. We had complete obstetric data in 85 pregnancies (78%), of which 76.5% progressed to live birth. Among these, 92.1% of postnatal echocardiograms concurred with antenatal ones. At 4 years old, 43.2% of offspring had no medical or developmental issues, 20.0% had mild medical or developmental issues, 21.5% had major medical or developmental issues, and 12.3% had deceased.

Conclusion: Fetal echocardiograms accurately diagnose CHDs. Future studies should evaluate the roles of chromosomal microarray and next-generation sequencing in diagnosing CHD.

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Keywords: cardiology, congenital heart disease, fetal anomaly, fetal echocardiography, fetal ultrasound, obstetric ultrasound, obstetrics and gynaecology, paediatrics

INTRODUCTION

Congenital heart diseases (CHDs) are the most common major congenital anomaly at up to 28%[1] and are responsible for 5.7% of all infant mortality.[2] While earlier studies in developed countries reported an overall CHD birth prevalence of 3.7–5.54 per 1000 live births,[3,4] more recent studies report a global and Asian birth prevalence of 9.1 and 9.3 per 1000 live births, respectively.[5] This rise in prevalence over time has been noted in other cohort studies[5,6] and has been attributed to better antenatal and postnatal diagnoses through advancements in echocardiography and better screening protocols, as previously severe cases were only diagnosed on autopsy.[5,7]

The birth prevalence of CHD in Singapore based on older studies is 9.07 per 1000 live births,[8,9] which corresponds with reported global and Asian rates.[5] In Singapore, standard antenatal ultrasound screening

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CLINICAL IMPACT

What is New

- The most common major fetal CHD subtypes were coarctation of aorta (17.4%), transposition of great arteries (16.5%), and tetralogy of Fallot and univentricular hearts (13.8% each).
- Upon confirmatory genetic testing, about a quarter were abnormal, where 22q microdeletion was the most common.
- Successful live births occurred in 76.5%. At age 4, 21.5% had major medical or developmental issues and 12.3% had deceased.

Clinical Implications

- Diagnosis of major fetal CHDs is associated with about a quarter having genetic abnormalities, major medical or developmental issues, or fetal demise.

includes a detailed second-trimester obstetric fetal anatomical scan between gestational age 18 and 22 weeks completed. This comprises cardiac assessment that incorporates a "5-transverse views" protocol visualising the abdominal situs, the 4-chamber view, each of the ventricular outflow tracts, and the 3-vessel and trachea view[10] of the developing fetal heart. The addition of a 3-vessel and trachea view to the usual 4-chamber view increases the sensitivity from 65.6% to 81.3% according to a prospective observational cohort study of 8,025 pregnancies.[11] Where an abnormality is detected or in patients with higher baseline risk, a referral is made to a paediatric cardiologist for fetal echocardiography and counselling on the postnatal prognosis and management options. Studies have demonstrated high concordance (96.1%) between cardiac evaluations during second-trimester fetal anatomical scans and fetal echocardiograms, especially where the aforementioned views were obtained.[12] Additionally, recent studies have demonstrated that fetal echocardiography has a high degree of specificity (approaching 99%) and sensitivity (40–60%) in diagnosing CHDs.[13,14]

This purpose of this study was to determine the distribution of major CHDs detected during routine antenatal fetal anomaly screening of a general obstetric population at a single centre, identify risk factors and genetic abnormalities and review their obstetric and postnatal outcomes.

METHOD

Population and disease

This was a single-centre retrospective cohort study that was approved by the Domain Specific Review Board, National Healthcare Group, Singapore with a waiver of informed consent (Reference Number 2018/00817). The study was performed between January 2014 and December 2017 at the Department of Obstetrics and Gynaecology, National University Hospital (NUH), a tertiary academic medical centre that conducts about 5000 deliveries per year. We reviewed the antenatal records for pregnancies where a major fetal CHD was diagnosed as part of routine screening. In cases with successful live birth at NUH, the child's medical records were reviewed to compare postnatal echocardiographic findings with the antenatal diagnosis and to determine short- and intermediate-term outcomes up to 4 years of age. Major CHD was defined as malformations of the heart and great arteries that typically require surgery or catheter-based intervention within the first year of life.[15,16] Included diagnoses were derived from Hoffman and Kaplan[17] and comprised (1) univentricular hearts (UVH), including hypoplastic left heart syndrome (HLHS); (2) transposition of great arteries (TGA); (3) truncus arteriosus; (4) interrupted aortic arch; (5) double outlet right ventricle (DORV); (6) tetralogy of Fallot, including pulmonary atresia and absent pulmonary valve; (7) pulmonary atresia with intact ventricular septum; (8) critical pulmonary valve stenosis; (9) tricuspid atresia; (10) Ebstein anomaly; (11) atrioventricular septal defect (AVSD); (12) large ventricular septal defect (VSD); (13) critical or severe aortic stenosis; and (14) coarctation of the aorta.

For this study, minor findings that were not associated with a discrete structural abnormality (e.g. pericardial effusion of less than 4 mm, fetal arrhythmias, intracardiac echogenic foci and cardiac axis deviation) or were unlikely to have major clinical significance and which were frequently missed (e.g. small VSDs and ASDs of less than 3 mm) were excluded.

Antenatal detection of CHD

If a major CHD was detected during obstetric fetal anatomical scans, a referral was made to a paediatric cardiologist for a detailed fetal echocardiogram[18] in the event that there was either (1) ambiguity in the initial diagnosis, or (2) the couple was keen to keep the pregnancy. This referral was not made if the couple was keen to terminate the pregnancy or follow-up elsewhere. Concordance between fetal echocardiograms and obstetric fetal anatomical scans was assessed after

reviewing scan reports and was defined as reaching the same major CHD diagnosis without missing any other major CHD. Discordance between obstetric fetal anatomic scans and fetal echocardiograms was defined as any discrepancy that may have an impact on postnatal clinical management and, therefore, affecting prenatal counselling.[19] While the fetal echocardiogram diagnosis is a higher level and more specialised scan compared to the fetal cardiac assessment in second-trimester obstetric fetal anatomical scan and is routinely taken to be the overriding antenatal diagnosis, in practice, major discordances are usually reconciled after discussion by the obstetrician and fetal cardiologist at our centre as part of the multidisciplinary discussion required to plan the antenatal and immediate postnatal care of these patients. Additionally, the gold standard reference remains the anatomic diagnosis on postnatal transthoracic echocardiogram. In the event of a complex CHD, the most severe cardiac abnormality was selected as the CHD subtype.

Aneuploidy screening and genetic tests

Aneuploidy screening was performed in either the combined first trimester screening (FTS) (which comprises nuchal translucency measurement plus serum PAPP-A and free β-hCG) or the non-invasive prenatal testing (NIPT) depending on the patient's choice. In the event of a high-risk result, couples were counselled on the next step, which was typically confirmatory invasive genetic testing. Some couples opted for contingent testing (i.e. following up a high-risk FTS result with NIPT testing).

Confirmatory antenatal genetic testing by amniocentesis or chorionic villus sampling (CVS) would be offered to identify aneuploidies or microdeletion disorders, such as 22q deletion syndrome. In most cases, the genetic testing offered comprised conventional karyotyping with 22q11 fluorescence in-situ hybridisation (FISH). In the latter years of this study period, chromosomal microarray analysis (CMA) or next-generation sequencing was increasingly offered. These fetuses would be followed up with serial, interval fetal cardiac imaging to assess progression, refine the diagnosis and plan for postnatal management. Upon live birth, a postnatal echocardiogram was performed within 24 hours of birth and compared with fetal echocardiograms. Where antenatal genetic testing had not been done, postnatal genetic testing would be offered by paediatricians or neonatologists.

Data collection

Based on a medical record review, demographic data (e.g. age and ethnicity), maternal risk factors for fetal CHD (e.g. diabetes mellitus, exposure to teratogenic drugs, family history), antenatal fetal anomaly scan and echocardiography results, aneuploidy screening details, and antenatal genetic testing results were collated. Data were presented either as means with standard deviation or frequencies with percentages (%), as appropriate. Outcomes of these pregnancies were classified as (1) termination of pregnancy (TOP), (2) pregnancy loss, (3) live birth, or (4) lost to follow-up. The mode of delivery was recorded. Postnatal echocardiograms, genetic tests and interventions were also collated. Outpatient records within NUH were reviewed for all offspring up to an age of 4 years to determine intermediate-term medical and developmental outcomes. These were classified as (1) no medical or developmental issues, (2) mild medical or developmental issues, or (3) major medical or developmental issues. Mild medical issues referred to situations where there was some medical impairment requiring continued regular outpatient monitoring but not requiring home oxygen therapy or frequent inpatient care. Major medical problems referred to situations where there was significant impairment to the child requiring either home oxygen therapy, non-invasive ventilatory support or frequent inpatient care. A mild developmental issue was a deficit in one developmental domain while major developmental issue referred to a deficit in 2 or more developmental domains.

RESULTS

Population

Over the study period, 20,031 pregnant patients (including multiple gestations) were screened for fetal anomalies at NUH, of which 109 (5.3 per 1000 pregnancies) were identified as having major CHDs (Fig. 1). Two cases were twin gestations. All cases were identified during standard obstetric fetal anatomical screening ultrasound scans between 18 and 22 gestational weeks. Findings on fetal echocardiograms by paediatric cardiologists were deemed concordant with fetal cardiac findings on obstetric fetal anatomical scans in 88.3% of cases. The mean age of women in the study population was 33.0 ± 4.5 years (Table 1). The rate of diabetes in pregnancy in the study population was 18.3%, of which 65% were gestational and 35% pre-existing. The rate of family or personal history of CHD was 4.6%. None of the patients in our cohort had other medical conditions (e.g. phenylketonuria) or teratogen exposure (e.g. anti-epileptics drugs, lithium or selective serotonin reuptake inhibitors) that predispose to fetal CHDs.

Among these 109 patients, we had complete obstetric data for 85 (78%) of cases, with the remaining 24 cases being lost to follow-up as their pregnancy outcomes

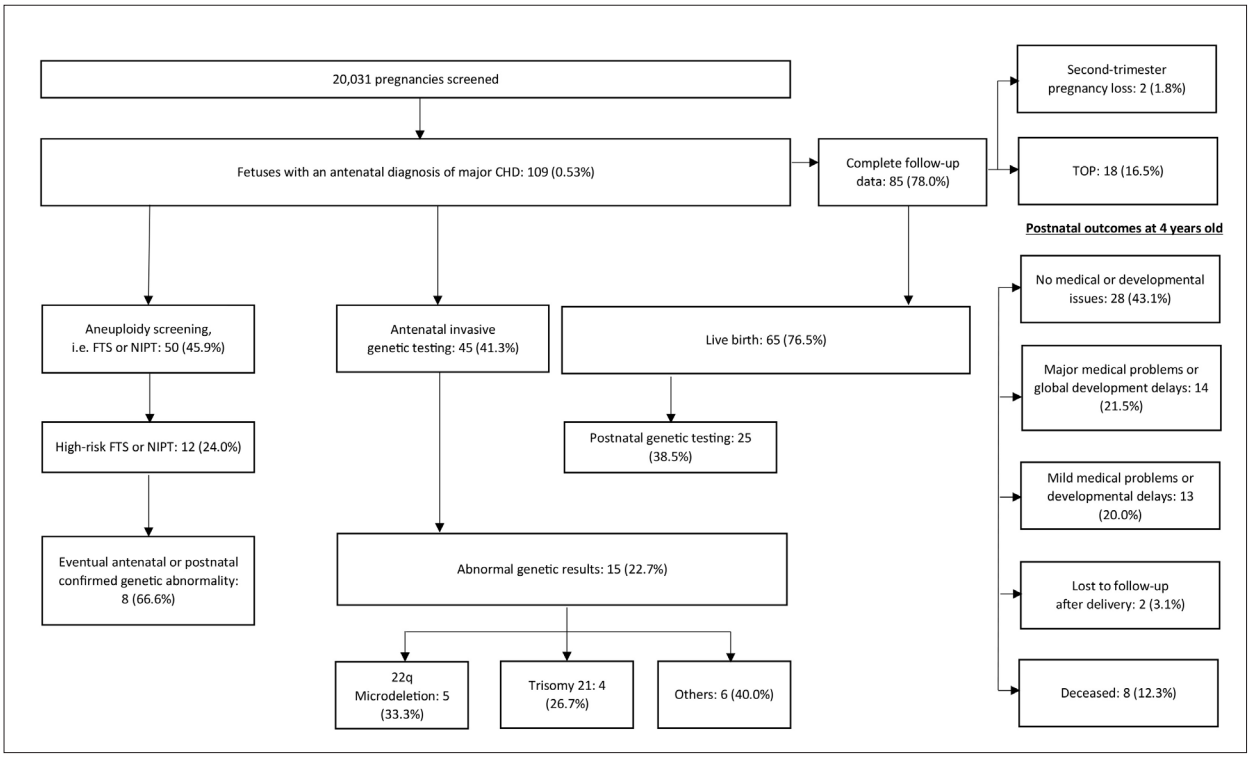

Fig. 1. Outcomes of the study population.
CHD: congenital heart disease, FTS: first trimester screening, NIPT: non-invasive prenatal testing, TOP: termination of pregnancy

Table 1. Demographic of the study population.

Sample size	109
Age, years	33.0 ± 4.5
Diabetes in pregnancy (%)	19 (17.4)
Gestational diabetes (%)	12 (63.2)
Pre-existing diabetes (%)	7 (36.8)
Family or personal history of CHD (%)	5 (4.6)
Ethnicity	
Chinese (%)	66 (60.6)
Malay (%)	18 (16.5)
Indian (%)	15 (13.8)
Others (%)	10 (9.2)
Complete follow-up data (until delivery or TOP)	85 (78.0)
Live birth (%)	65 (76.5)
TOP (%)	18 (21.2)
Second-trimester pregnancy loss (%)	2 (2.4)
Postnatal death (%)	8 (9.4)
Lost to follow-up	24 (22.0)

CHD: congenital heart disease, TOP: termination of pregnancy
Values represent mean ± standard deviation or frequency (percentage)

could not be ascertained (Table 1). Twenty of the 85 cases (23.5%) either underwent termination of pregnancy or resulted in pregnancy loss, and 65 (76.5%) progressed to live births. Of these 65 live births, 63 had postnatal echocardiograms of which 92.1% were deemed concordant with antenatal fetal echocardiograms.

Distribution of CHDs

Among the 109 CHDs (Table 2 and Fig. 2), 57.8% (63 in 109) were cyanotic. Specifically, 44.0% (48 in 109) were conotruncal abnormalities (i.e. TGA, tetralogy of Fallot, DORV and truncus arteriosus), 13.8% (15 in 109) were UVH (i.e. single ventricles, HLHS, or heterotaxy syndrome), 17.4% (19 in 109) were coarctation of aorta, 3.7% (4 in 109) were tricuspid atresia and 2.8% (3 in 109) were critical or severe aortic stenosis. Finally, critical pulmonary valve stenosis, AVSD and large isolated VSDs comprised 5.5% (6 in 109) each. Of the 109 cases, 12.8% (14 in 109) had extracardiac abnormalities. Genetic testing was performed in 11 of these 14 cases, of which 5 were abnormal (Table 3).

Obstetric and postnatal outcomes

Of the 85 cases that had complete follow-up data, 21.2% (18 in 85) underwent termination of pregnancy, 2.4% (2 in 85) sustained a second-trimester pregnancy loss, and

Table 2. Distribution of major congenital heart disease, genetic diagnoses and their outcomes (n=109).

Type of CHD	n (%)	Antenatal diagnosis							Outcome			
		Aneuploidy screening (i.e. FTS or NIPT)		Confirmatory genetic testing (i.e. Amniocentesis, CVS, or postnatal)		Extracardiac fetal anomaly (%)	Fetal echocardiography		Lost to follow-up (%)	Second-trimester pregnancy loss (%)	TOP (%)	Live birth	
		Number	High risk (%)	Number	Abnormal (%)		Performed	Concordance* (%)				Number (%)	Neonatal outcome
TGA	18 (16.5)	**Total:** 8 **FTS:** 2 **NIPT:** 3 **Cont:** 3	0 (0)	**Total:** 10 **AN:** 6 **PN:** 4	0 (0)	4 (22.2)	12	12 (100.0)	5 (27.8)	0 (0)	2 (11.1)	11 (61.1)	**A:** 0 **B:** 3 **C:** 0 **D:** 7 **E:** 1
DORV	10 (9.2)	**Total:** 5 **FTS:** 3 **NIPT:** 1 **Cont:** 1	2 (40)	**Total:** 5 **AN:** 3 **PN:** 2	1 (20.0)	0 (0)	4	3 (75.0)	3 (30.0)	0 (0)	2 (20.0)	5 (50.0)	**A:** 1 **B:** 0 **C:** 1 **D:** 3 **E:** 0
Tetralogy of Fallot	15 (13.8)	**Total:** 5 **FTS:** 2 **NIPT:** 3 **Cont:** 0	5[§] (100)	**Total:** 14 **AN:** 11 **PN:** 6[†]	6 (42.9)[‡]	4 (26.7)	13	10 (76.9)	2 (13.3)	0 (0)	3 (20.0)	10 (66.7)	**A:** 1 **B:** 2 **C:** 6 **D:** 1 **E:** 0
Truncus arteriosus	5 (4.6)	**Total:** 1 **FTS:** 1 **NIPT:** 0 **Cont:** 0	0 (0)	**Total:** 4 **AN:** 4 **PN:** 0	1 (25.0)	1 (20.0)	3	3 (100.0)	1 (20.0)	0 (0)	2 (40.0)	2 (40.0)	**A:** 2 **B:** 0 **C:** 0 **D:** 0 **E:** 0
Interrupted aortic arch	2 (1.8%)	**Total:** 0 **FTS:** 0 **NIPT:** 0 **Cont:** 0	-	**Total:** 0 **AN:** 0 **PN:** 0	-	0 (0)	0	-	1 (50.0)	0 (0)	1 (50.0)	0 (0)	**A:** 0 **B:** 0 **C:** 0 **D:** 0 **E:** 0
Coarctation of aorta	19 (17.4)	**Total:** 10 **FTS:** 5 **NIPT:** 3 **Cont:** 2	1 (10.0)	**Total:** 10 **AN:** 7 **PN:** 3	1 (10.0)	0 (0)	12	10 (83.3)	4 (21.1)	0 (0)	0 (0)	15 (78.9)	**A:** 2 **B:** 3 **C:** 4 **D:** 6 **E:** 0
UVH	15 (13.8)	**Total:** 6 **FTS:** 4 **NIPT:** 1 **Cont:** 1	0 (0)	**Total:** 6 **AN:** 5 **PN:** 1	1 (16.7)	1 (6.67)	7	7 (100.0)	5 (33.3)	1 (6.67)	6 (40.0)	3 (20.0)	**A:** 1 **B:** 1 **C:** 0 **D:** 0 **E:** 1

Table 2. Distribution of major congenital heart disease, genetic diagnoses and their outcomes (n=109). (Cont'd)

Type of CHD	n (%)	Antenatal diagnosis							Outcome				
		Aneuploidy screening (i.e. FTS or NIPT)		Confirmatory genetic testing (i.e. Amniocentesis, CVS, or postnatal)		Extracardiac fetal anomaly (%)	Fetal echocardiography		Lost to follow-up (%)	Second-trimester pregnancy loss (%)	TOP (%)	Live birth	
		Number	High risk (%)	Number	Abnormal (%)		Performed	Concordance* (%)				Number (%)	Neonatal outcome
Critical pulmonary valve stenosis	6 (5.5%)	**Total:** 4 **FTS:** 3 **NIPT:** 0 **Cont:** 1	0 (0)	**Total:** 4 **AN:** 3 **PN:** 1	0 (0)	0 (0)	5	5 (100.0)	1 (16.7)	0 (0)	0 (0)	5 (83.3)	**A:** 0 **B:** 2 **C:** 0 **D:** 3 **E:** 0
AVSD	6 (5.5%)	**Total:** 4 **FTS:** 1 **NIPT:** 3 **Cont:** 0	2 (40.0)	**Total:** 4 **AN:** 1 **PN:** 3	3 (75.0)	2 (33.3)	5	5 (100.0)	1 (16.7)	0 (0)	0 (0)	5 (83.3)	**A:** 1 **B:** 0 **C:** 1 **D:** 3 **E:** 0
Large ventricular septal defect	6 (5.5%)	**Total:** 2 **FTS:** 1 **NIPT:** 1 **Cont:** 0	0 (0)	**Total:** 4 **AN:** 2 **PN:** 2	1 (25.0)	1 (16.7)	5	5 (100.0)	1 (16.7)	0 (0)	0 (0)	5 (83.3)	**A:** 0 **B:** 1 **C:** 1 **D:** 3 **E:** 0
Tricuspid atresia	4 (3.7%)	**Total:** 3 **FTS:** 3 **NIPT:** 0 **Cont:** 0	2 (66.7)	**Total:** 3 **AN:** 2 **PN:** 2†	1 (33.3)	1 (25.0)	2	1 (50.0)	0 (0)	1 (25.0)	1 (25.0)	2 (50.0)	**A:** 0 **B:** 1 **C:** 1 **D:** 0 **E:** 0
Critical or severe aortic stenosis	3 (2.8%)	**Total:** 2 **FTS:** 1 **NIPT:** 1 **Cont:** 0	0 (0)	**Total:** 2 **AN:** 1 **PN:** 1	0 (0)	0 (0)	2	1 (50.0)	0 (0)	0 (0)	1 (33.3)	2 (66.7)	**A:** 0 **B:** 0 **C:** 0 **D:** 2 **E:** 0
Total	109	**Total:** 50 **FTS:** 26 **NIPT:** 16 **Cont:** 8	12 (24.0)	**Total:** 66 **AN:** 45 **PN:** 25†	15 (23.1)	14 (12.8)	70	62 (88.6)	24 (22.0)	2 (1.8)	18 (16.5)	65 (59.6)	**A:** 8 **B:** 13 **C:** 14 **D:** 28 **E:** 2

AN: antenatal, AVSD: atrioventricular septal defect, Cont: contingent, CVS: chorionic villus sampling, DORV: double outlet right ventricle, FTS: first trimester screening, NIPT: non-invasive prenatal testing, PN: postnatal, TGA: transposition of great arteries, TOP: termination of pregnancy, UVH: univentricular hearts

A: infant death, **B**: mild medical/developmental issues, **C**: major medical or developmental issues, **D**: no medical or developmental issues, **E**: postnatal lost to follow-up

***** Where formal fetal echocardiography was performed, concordance was met when the obstetric fetal anatomical scan made the same major CHD diagnosis without missing any other major CHD

† Three cases of tetralogy of Fallot and one case of tricuspid atresia underwent postnatal genetic testing in addition to antenatal invasive genetic testing for the purpose of additional genetic testing

‡ One case of tetralogy of Fallot had a variant of unknown significance on chromosomal microarray analysis. These variants were also detected in phenotypically normal parents.

§ One aneuploidy screening result was deemed high risk, as it comprised two consecutive inconclusive NIPT results.

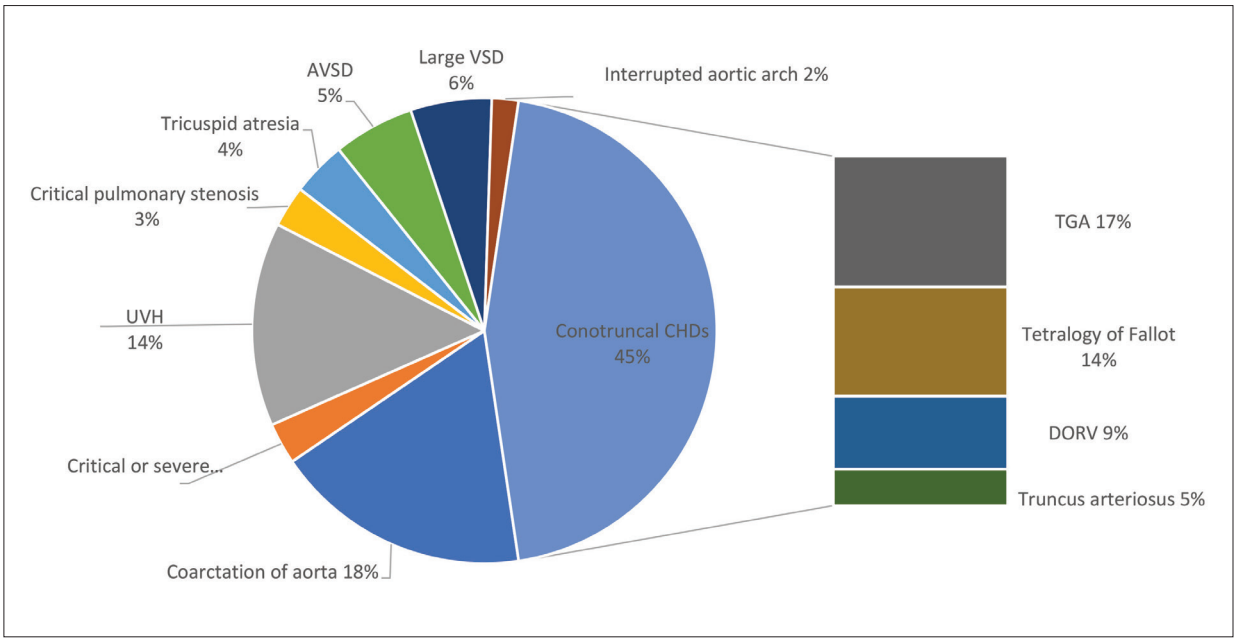

Fig. 2. Distribution of major congenital heart diseases.
AVSD: atrioventricular septal defect, CHD: congenital heart disease, DORV: double outlet right ventricle, TGA: transposition of great arteries, UVH: univentricular hearts, VSD: ventricular septal defect

Table 3. Fetuses with congenital heart diseases and extracardiac abnormalities.

Congenital heart disease	Extracardiac anomaly	Genetic diagnosis
TGA	CCAM	Amniocentesis karyotype: normal
TGA	CCAM	Amniocentesis karyotype: normal
TGA	Abdominal situs inversus	Genetic test not performed
TGA	Bilateral cleft lip and palate	Postnatal karyotype: normal
Truncus arteriosus	Left multicystic kidney	Amniocentesis karyotype: normal
Tetralogy of Fallot	Ectopia cordis	Amniocentesis karyotype: normal
Tetralogy of Fallot	Bilateral talipes equinovarus	Lost to follow-up
Tetralogy of Fallot	Epilepsy, global developmental delay, centra hypotonia, central apnoea, nystagmus, hepatomegaly, supernumerary nipples	Postnatal chromosomal microarray: benign familial copy variants WES: homozygous mutation in PIGN causing congenital disorder of glycosylation
Tetralogy of Fallot	1) Spinal angulation at thoracic level 2) Dysmorphic facies with micrognathia	Amniocentesis karyotype: normal
Tricuspid atresia	Right ulnar dysplasia/hypoplasia with intrauterine growth restriction	Amniocentesis karyotype: 46,XX,der(21)ins(21;?)(q11.2;?)
UVH	Abdominal situs inversus	Lost to follow-up
AVSD	Inferior cerebellar vermian hypoplasia	Postnatal karyotype: trisomy 21
AVSD	Bilateral adducted fourth toe	Postnatal CMA: duplication of 444 kb in 15q13.3 encompassing part of *CHRNA7* gene. Known to have variable penetrance and not associated with AVSD. No parental CMA.
Large ventricular septal defect	Right talipes equinovarus	Postnatal karyotype: normal. FISH: 22q deletion detected

AVSD: atrioventricular septal defect, CCAM: congenital cystic adenomatoid malformation, CMA: chromosomal microarray analysis, FISH: fluorescence in-situ hybridisation, TGA: transposition of arteries, UVH: univentricular hearts, WES: whole exome sequencing

76.4% (65 in 85) were live births (Table 2 and Fig. 1). Of the 65 live births, 56.9% (37 in 65) were delivered via caesarean section with the remaining via normal vaginal delivery. Among the liveborn neonates, 72.3% (47 in 65) underwent postnatal cardiac intervention. At 4 years of follow-up, 43.2% (28 in 65) had no medical or developmental issues, 20.0% (13 in 65) had mild medical or developmental issues, and 21.5% (14 in 65) had major medical or developmental issues. Additionally, 12.3% (8 in 65) had deceased (at an average of 6.9 months of age), and 3.1% (2 in 65) were lost to follow-up.

Aneuploidy screening

Aneuploidy screening by FTS or NIPT had been performed in 45.9% (50 in 109) cases prior to the diagnosis of a major fetal CHD (Fig. 1). Of these, 52% (26 in 50) and 32% (16 in 50) were primary screening by FTS and NIPT, respectively, while 16% (8 in 50) were cases where couples opted for contingent NIPT as opposed to invasive testing after being counselled for high-risk or inconclusive FTS results. Of the 50 aneuploidy screenings performed, 24.0% (12 in 50) were high-risk results (FTS: 6; primary NIPT: 5; contingent NIPT: 1). Among these 12 high-risk results, 9 underwent confirmatory antenatal genetic testing with conventional karyotyping and FISH (2 CVS and 7 amniocentesis). Three were abnormal: 1 trisomy X, 1 22q11 microdeletion and 1 46 XX with an unbalanced insertion of unidentifiable material in the long arm of chromosome 21. Among the remaining 3 high-risk results where confirmatory antenatal testing was not performed, postnatal genetic testing revealed 2 cases of trisomy 21. Thus, among the 12 high-risk aneuploidy screening results, a total of 5 (41.7%) had a confirmed abnormal genetic diagnosis.

Confirmatory genetic testing

Out of the 109 cases of fetal CHD, 41.3% (45 in 109) had antenatal genetic testing by amniocentesis (43) or CVS (2). Nine were indicated by high-risk aneuploidy screening results, as described above, while the rest were indicated by findings of fetal CHD. Of the cases that underwent antenatal genetic testing, 60.0% (27 in 45) had not undergone any aneuploidy screening prior and 17.8% (8 in 45) had high-risk results. Of the 45 who had antenatal genetic testing, 42 underwent conventional karyotyping with FISH for 22q, 2 underwent CMA only and 1 underwent both CMA and whole exome sequencing (WES). Abnormal results were obtained in 17.7% (8 in 45) and are discussed below. Of the 65 live births, 38.4% (25 in 65) had postnatal genetic testing of which all except 3 were conventional karyotyping with FISH for 22q (2 were CMA, 1 was both CMA and WES). Seven had abnormal results and are discussed below.

Out of the 109 cases of fetal CHD, 60.5% (66 in 109) underwent either antenatal or postnatal confirmatory genetic testing (4 cases with antenatal genetic testing also underwent other forms of postnatal genetic testing). Of these, 22.7% (15 in 66) had abnormalities. The following abnormalities were found on conventional karyotyping and FISH for 22q11 microdeletion: 5 22q11 microdeletion (2 tetralogy of Fallot, 1 DORV, 1 truncus arteriosus, 1 VSD); 4 trisomy 21 (2 AVSD, 1 tetralogy of Fallot, 1 univentricular heart); 1 trisomy X (tetralogy of Fallot); 1 monosomy X (coarctation of aorta); and 1 unbalanced insertion of unidentifiable material in long arm of chromosome 21 (tricuspid atresia in 1 twin of a dichorionic, diamniotic pair). Three cases had abnormal CMA results. One fetus with an AVSD had an abnormal postnatal CMA result showing a pathogenic 444 kb duplication in 15q13.3, encompassing part of the *CHRNA7* gene. While AVSDs have been reported with 15q13.3 microdeletions,[20] it has a highly variable clinical spectrum ranging from non-pathogenic to severe phenotype. Parental testing was not performed in this case to determine if it was de novo or inherited. For 1 fetus with tetralogy of Fallot, while antenatal CMA was normal, additional postnatal genetic testing was performed due to the presence of extracardiac defects, such as spinal angulation at the thoracic vertebrae and micrognathia and a previous termination of pregnancy for a fetus with multiple fetal anomalies. A postnatal expanded CMA panel only revealed benign familial copy number variants, and a next-generation sequencing panel for genes associated with skeletal malformations was unremarkable. WES revealed an inherited homozygous mutation in the PIGN gene causing a congenital disorder of glycosylation. Finally, 1 fetus with a tetralogy of Fallot had a variant of unknown significance with a 7p21.2 duplication of 453 kb and 7p21.1 duplication of 434 kb. While associated with macrosomia and a mild bowel dilation in literature, this was deemed to be a benign familial copy number variant as this was seen in the normal parent as well.

DISCUSSION

This is a longitudinal cohort study in 109 pregnancies with antenatally diagnosed major CHDs that stratifies outcomes by the type of CHD and reports their associated extracardiac anomalies, genetic tests, obstetric outcomes and developmental and health outcomes at 4 years of age. There was a high concordance between obstetric fetal anatomical scans and fetal echocardiography in the characterisation of major CHDs (88.6%). At 4 years

postnatally, 43.2% had no medical or developmental issues while 21.5% had major medical problems of global developmental delay and 12.3% deceased. Such data have been further presented stratified by the type of major CHD. We were able to report on the results of genetic testing, mostly via conventional karyotyping and FISH for 22q microdeletion in 60.5% of cases, and found that about a quarter had abnormalities. The most common genetic abnormality was a 22q microdeletion followed by trisomy 21. Overall, 59.6% of our patients progressed to live birth. Our cohort had a loss to follow-up rate of 22.0% (24 in 109) at the time of delivery and a further 3.1% after delivery (2 in 65).

The prevalence of major CHD in our study cohort was 5.3 per 1000 pregnancies screened at our centre. This value lies within figures provided by two other studies in Singapore; a single-centre study involving euploid fetuses conducted between 2008 and 2009 (2.7 per 1000 fetuses)[18] and a national study involving live births between 1994 and 2000, which also included minor CHDs (8.12 per 1000 live births and stillbirths)[9] (Fig. 3). Comparison with the former study was limited, as it excluded fetuses with abnormal karyotype, which accounted for 9.09% (6 in 66) of our cases that underwent confirmatory genetic testing. The latter study evaluated birth defects reported to the National Birth Defects Registry after delivery (live birth or stillbirth) and abortion. A likely reason for an overall higher incidence of CHDs in Tan KH et al. (3.37 vs 0.30 per 1000) may be the inclusion of small VSDs based on postnatal diagnosis which are frequently not seen on fetal echocardiogram, do not require intervention, and may spontaneously close. Among other major CHDs, such as tetralogy of Fallot, HLHS or UVH, transposition of great arteries and truncus arteriosus, our cohort reported higher incidence rates than Tan KH et al., although this may be due to a selection bias as our hospital is a national referral centre for complicated fetal anomalies.

While Asia has the highest birth prevalence of CHDs (9.3 per 1000 live births[5]), significant inter-regional variations exist likely due to differences in factors such as nutrition,[6] consanguinity,[21] maternal age,[22] ethnicity,[9] abortion patterns,[23] temporal changes in CHD prevalence,[5] availability of accurate fetal diagnosis[5,7] and differences in reporting standards. Our cited prevalence is similar to that cited in a recent

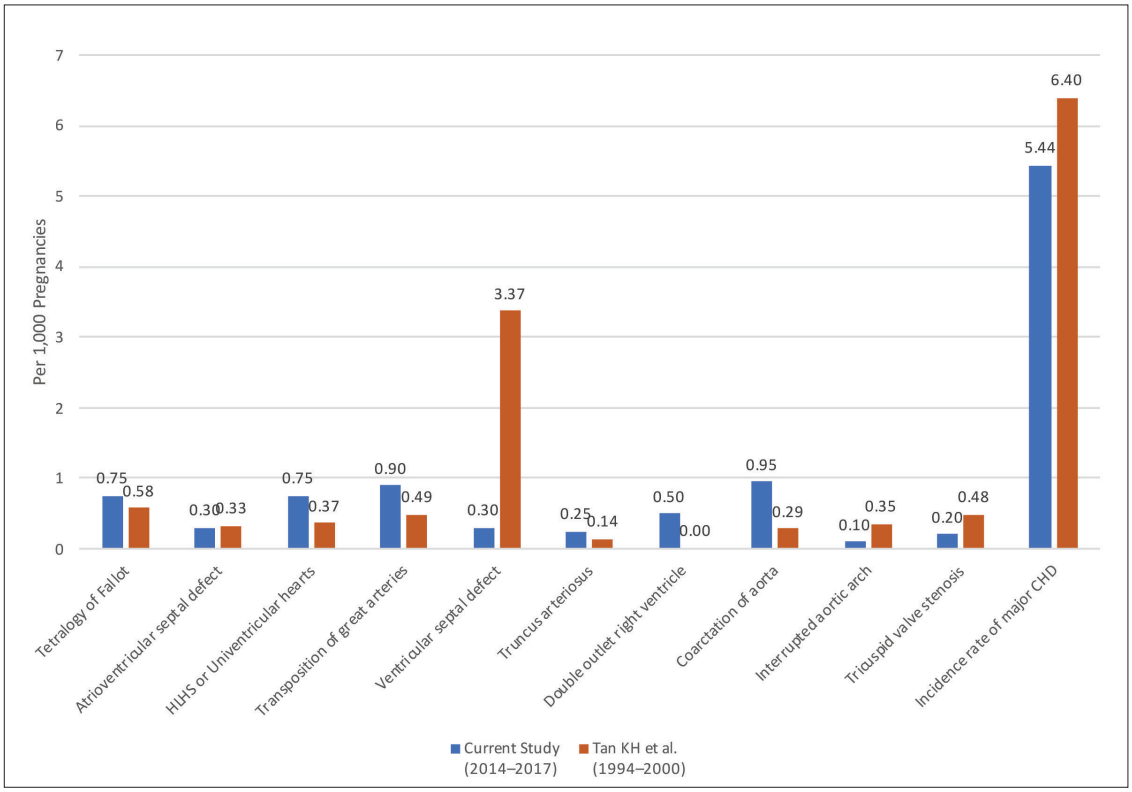

Fig. 3. Comparisons in prevalence of major congenital heart disease between the current study (2014–2017) and a historical cohort, i.e. Tan KH et al.[9] (1994–2000).

extensive systematic review involving European populations (6.51 per 1000 fetuses[6]), although a higher proportion were conotruncal abnormalities (44.0% vs 20%). This may also be due to a selection bias arising from our centre's status as a major referral centre for complicated fetal anomalies.

While confirmatory antenatal genetic testing is recommended when 1 or more major fetal structural abnormalities are detected,[24] only 41.3% of our cohort underwent this, of which 18.3% found genetic abnormalities. CMA is currently recommended as a first-line test for isolated fetal anomalies, as submicroscopic copy number variants have been detected in up to 4.6% of cases with isolated fetal CHDs and normal karyotypes.[25] In our cohort, while only 6.67% of fetuses underwent antenatal CMA, this is likely because professional consensus for this was only formed from 2016 onwards,[24] i.e. in the latter years of this study's inclusion window. Two other factors, which may have lowered uptake during the timeframe of this study, included lack of government subsidy for CMA and NGS as well as minimal access to professional genetic counsellors, a feature that has been associated with increased uptake of genetic tests.[26-28] Both factors have been addressed in recent years, and a more updated study would likely give a better understanding of the genetic diagnosis associated with major fetal CHDs.

With increasing affordability and accessibility, next-generation sequencing techniques, such as WES, will grow in importance in evaluating fetal anomalies.[29] Two large cohort studies[30,31] and a recent meta-analysis[32] have demonstrated that 5–11.1% of fetuses with CHDs and a normal karyotype or CMA had diagnostic genetic variants on WES with higher yields in multisystem fetal anomalies. As 65.4% of the diagnostic genetic variants were associated with learning disability,[31] genetic counselling is increasingly a critical adjunct to a fetal cardiac service[33,34] to help weigh decisions for the nature of tests to be done, continue pregnancy and allay parental anxiety.[35]

While earlier studies did not demonstrate a significant mortality benefit associated with the antenatal diagnosis of CHDs,[36,37] more recent meta-analyses[38,39] have shown significant reduction in invasive respiratory support,[40] fewer perioperative neurologic events and earlier initiation of prostaglandin E1 therapy[41] likely as a result of improved antenatal counselling, better coordination of delivery resources[42] and facilitation of postnatal care and procedural planning.[43] Furthermore, accurate antenatal diagnosis will play an important role in facilitating nascent fetal cardiac interventions, such as aortic valvuloplasties, to prevent progression of aortic stenosis into HLHS.[44]

Strengths and limitations

To the best of the researchers' knowledge, this historical cohort study of fetal CHDs is the largest reported in Singapore. While local birth registry data have been published,[8,9] we have not explored other aspects, such as demographics, sonographic and echocardiographic diagnoses; aneuploidy screening results; extracardiac abnormalities; genetic testing results; postnatal findings; and intermediate-term outcomes. We believe this study serves as a baseline for other local and regional studies. As the outcomes of our study have been stratified according to the type of CHD, this research aids counselling of parents at the time of fetal CHD diagnosis. We also believe our study establishes a framework for reporting and auditing outcomes of a fetal CHD screening programme with charting of outcomes from the time of antenatal diagnosis until 4 years old.

A major limitation in our cohort was the low uptake of CMA despite being a first-line test for fetal anomalies. This was likely due to cost considerations, as CMA was not covered by either government co-payment or most insurance providers. Utilising CMA, as opposed to karyotyping as a first-line test, was also gaining acceptance around the duration of this cohort. Further studies to understand factors that contribute to patient acceptability of antenatal genetic tests should be conducted. Another limitation of our study was a significant loss to follow-up rate of 22.0% during pregnancy. Given that the expertise and availability of advanced paediatric cardiac services are primarily in tertiary public health institutions in Singapore, it is likely that most of these cases switched to local private or overseas healthcare institutions for terminations of pregnancy either for privacy reasons, cost savings, or due to Singapore's legal limits for termination of pregnancy being at the gestational age of 24 weeks completed. As our study's inclusion criteria involved fetal CHDs detected antenatally, there is a possibility that missing CHDs are detected only postnatally either due to false negative screening at the fetal anatomical scan or poor antenatal follow-up. While this population is anecdotally thought to be very small, reviewing paediatric cardiac databases would eliminate this ambiguity and contribute to more holistic conclusions. Finally, given that single-centre studies are susceptible to selection biases, major CHDs may also have been potentially over-represented at our centre, which is a referral site for complex fetal FAs. Nevertheless, to our knowledge,

there is no formal database at a national-level or in other health institutions that includes our study parameters to readily facilitate comparison.

Further research

To mitigate some of the above limitations, a population-based approach involving a national birth defect registry linking genetic diagnosis, extracardiac findings and long-term outcomes would permit a more holistic understanding of the true distribution of fetal CHDs and temporal epidemiologic trends. Additionally, multicentre data would facilitate an audit assessing the effectiveness of current antenatal birth defect screening policies in detecting fetal CHDs early and accessibility of confirmatory genetic tests to interested parents. A more contemporary study would also capitalise on the rising accessibility to antenatal genetic diagnosis through CMA and NGS as well as professional genetic counselling to allow a more updated understanding of the relationship between fetal CHD and genetic abnormalities.

CONCLUSION

The accuracy of fetal anatomical scans and echocardiography in detecting major CHD is high with good concordance between prenatal and postnatal diagnoses. As CHD is the most common fetal anomaly[1] and with 22.7% being associated with genetic abnormalities, fetal CHD diagnosis may increasingly serve as a gateway for antenatal genetic diagnoses. High-quality genetic counselling and testing is essential. A repeat study with a similar format involving present-day practices, which include CMA and next generation sequencing (e.g. WES), would help develop local guidelines for counselling CHD.

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Breast conservation treatment and frozen section analysis of margins

Dear Editor,

Re. Surgical margins assessment reduces re-excision rates in breast-conserving surgery

I read with interest the article by Woon et al. published in a recent issue of the *Annals* on the reduction of re-excision rates with the use of intraoperative frozen section (FS) analysis.[1] This certainly has the potential to improve patient outcomes after surgery as their study has demonstrated. It is also likely that a decrease in re-operation rates would have a positive influence on patients' choice to undergo breast conservation treatment (BCT) rather than mastectomy.

However, there are a few points made in this letter by Woon et al. that merit further discussion. The authors cite an article by Fisher et al. published in 2002.[2] This was a report on a 20-year follow-up of a randomised controlled trial (RCT), which did indeed show equivalent survival following both BCT with radiotherapy and mastectomy. However, in this report, local recurrence following BCT was reported to be numerically lower than after mastectomy.[2] In Table 2 of the report, it is listed that local recurrence with lumpectomy and radiotherapy was 2.7% while that for mastectomy was 10.2%. Having cited this report in the context of survival, the authors of the letter proceeded to comment that breast conserving surgery is associated with higher local recurrence risk, which may appear contradictory. It should also be noted that this report by Fisher et al. that was cited as a source on higher local recurrence with BCT was based on follow-up information up through 2001. There are more recent studies that demonstrate similar, if not lower local recurrence rates with BCT compared to mastectomy.[3]

In addition, while it is true that the National Surgical Adjuvant Breast and Bowel Project B-06 study was an RCT, there is now a significant body of contemporary evidence to suggest that BCT may confer superior survival compared to mastectomy. One of the earliest studies was by Martin et al.[4] in 2007 and more recently, a large study by De la Cruz et al. published in 2022.[5] Another study reported an overall and breast cancer-specific relative survival gain of 56% to 70% in node-negative patients who underwent BCT compared with those who underwent mastectomy.[6] This information is relevant for treatment selection and can perhaps provide an alternative view to the long-held but possibly imprecise belief that BCT and mastectomy result in comparable long-term survival rates, which the authors had expressed.

Time efficiency is a laudable objective. However, this should not supplant good surgical oncology principles. Unless surgeons plan to change instruments intraoperatively, it would be in line with oncologic principles to perform sentinel lymph node biopsy (SLNB) first, as this is more likely to be an unaffected ("clean") operative field, rather than to perform the wide excision first, where instruments may be contaminated with tumour cells. Having performed SLNB first, the sentinel node may also be sent for FS, which would further contribute to a decrease in re-operation rates. Hence, there may be minimal time advantage in performing the wide excision part of the surgery first as the authors have proposed.

Finally, it is possible to further reduce re-excision rates using appropriate techniques.[7] As the authors have alluded in their article, reduction of re-excision rates improves the patient treatment experience, and I agree that the additional cost and resources required for the routine conduct of FS is likely in totality to be lower than allowing higher re-operative rates without customary intraoperative margin assessment. It is therefore an approach that should be applied until there is clear evidence that another strategy offers better outcomes in terms of cost-effectiveness and surgical results. In this respect, oncoplastic breast surgery may not be the answer, as it contributes to higher resource utilisation, surgical morbidity, and might not serve as a cost-effective means of optimal treatment and appropriate surgical de-escalation.[8]

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Dear Editor,

Re. Authors' reply

We would like to thank the reader for the interest in our article[1] and pertinent points raised. First, in relation to the citation of Fisher et al., the reader highlighted that reporting local recurrence rate as being lower for mastectomy compared to breast conservation treatment (BCT) would be contradictory based on Table 2 of this article.[2] In this table, local recurrence with lumpectomy and radiotherapy was reported as 2.7% compared to 10.2% for mastectomy. It should be noted however that a caveat under this table stated that tumours in the ipsilateral breast after lumpectomy were not considered recurrences, and women in the lumpectomy groups who had such tumours were classified as event-free. Fisher et al. had separately outlined in Figure 1 of their article, the cumulative incidence of a recurrence in the ipsilateral breast 20 years after surgery at 14.3% among the women who underwent irradiation after lumpectomy.

Similarly, another 20-year follow-up of a randomised trial by Veronesi et al. comparing breast conserving surgery with radical mastectomy for early breast cancer also showed a lower cumulative recurrence at 2.3% for the radical mastectomy group compared to 8.8% in the BCT group, though comparable overall survival and breast cancer-specific survival.[3] The strength of both studies with respect to local recurrence and survival lies in their long duration of follow-up of 20 years.

However, we acknowledge the views of the reader that contemporary data from recent studies have been promising, with evidence to suggest that BCT could confer comparable local recurrence rates[4] to mastectomy with reasons postulated to be multifactorial due to improvements in diagnostic imaging, pathologic margins assessment, precision of radiation therapy delivery, and effectiveness of systemic and targeted therapy. However, before more long-term data are made available, we prefer to interpret these results with caution. Furthermore, our study is also not designed to compare and address this issue of differences in recurrence rates between BCT and mastectomy.

Second, we applaud the reader for highlighting the need to observe important oncological principles in the conduct of surgery. We acknowledge the theoretical concern of seeding of tumour cells by performing lumpectomy first, followed by sentinel lymph node biopsy. However, this is perhaps analogous to the similar theoretical risk of tumour seeding with preoperative core needle biopsy, which has also not been shown to increase local recurrence rate in breast cancer patients.[5] The reason for proposing to perform the lumpectomy first and assess the margins before sentinel lymph node biopsy is that in our experience, frozen section (FS) assessment of margins generally takes longer compared to sentinel lymph node biopsy. However, a change of instruments as suggested by the reader can mitigate the risk of tumour seeding.

Finally, while we appreciate the reader's concurrence that intraoperative FS analysis of margins is a valuable technique to decrease re-operation rates, we remain cognisant of the logistical challenges and added pathologist involvement as practical considerations that one may face on the ground. As such, other techniques such as cavity shaving[6] and oncoplastic techniques,[7] which have also been shown to decrease positive margins rate deserve mention. Additionally, the choice of technique is best personalised to the individual surgeon's expertise and the healthcare setting. Oncoplastic surgery and FS analysis of margins are not mutually exclusive. Oncoplastic surgery utilised selectively in the appropriate context of large tumour or multifocal ductal carcinoma in situ remains an invaluable tool for the breast surgeon to achieve clear margins while preserving cosmesis for breast cancer patients.

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LETTER TO THE EDITOR

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Managing and preventing severe hand injuries among sugarcane juicer operators

Dear Editor,

Of all hand injuries encountered at an emergency department, 54% are sustained in the workplace,[1] in part contributed by occupational injuries among food and beverage operators that caused a loss of 16,197 man-hours in 2021 alone.[2] Commonplace in Singapore and in parts of South and Southeast Asia is the sugarcane juicer, a machine typically operated by sole proprietorship drink stalls within food centres and more importantly, a dangerous cause of workplace accidents. We highlight the severity of sugarcane juicer-related hand injuries that have resulted in permanent disabilities in 3 representative patients. We also review occupational health risks of such technology to understand the contributing factors involved and how they can be prevented.

Three patients, 2 in their 50s and a teenager, were managed for mutilating hand injuries from operating the sugarcane juicer. The teenage girl (patient A) and one of the older women (patient B) injured their dominant right hand while cleaning the machine without switching it off. They sustained extensive degloving injuries and avulsion amputations of all fingers except for the ring and little fingers in patient A's case, and the little finger in patient B's case. Patient C used the juicer without its safety guard so that more sugarcane stems could be fed inside, and sustained a left mangled hand. She suffered comminuted fractures in her index, middle, ring and little fingers; a thumb avulsion amputation and a proximal degloving skin injury. For all 3 patients, initial management involved debridement and amputation of the unsalvageable digits. Eventual resurfacing of their wounds required complex flap reconstruction—an extended lateral arm flap, bi-lobed pedicled groin flap and posterior interosseous artery flap. Patient A had a total of 10 surgeries to regain a basic hand consisting of a toe-to-thumb transfer and 2 digits. Patient B underwent a total of 13 surgeries to restore an opposable thumb and 2 digits involving staged creation of the webspace with a flap, and thumb lengthening. Patient C also underwent digit lengthening and first webspace reconstruction. Nine surgeries were performed to obtain an opposable thumb and a mitten hand appearance.

The resultant percentage of disability in these mutilating hand injuries ranged from 30% for complete thumb loss to 70% when all 5 digits are involved (cases 2 and 3) according to A Guide to the Assessment of Traumatic Injuries and Occupational Diseases for Work Injury Compensation published by the Singapore Ministry of Manpower. None of our patients returned to pre-injury level of work activity.

Sugarcane roller injuries have a high morbidity due to the following unique yet destructive characteristics. First, unlike a typical roller press, serrations on sugarcane rollers exert a firm grip and generate high compressive and forward tractional forces that crush, deglove and avulse a wide area of skin, neurovascular bundles, tendon and bones.[3,4] Second, sugarcane machine rollers are positioned with a gap that allows the level of injury to extend proximally to the metacarpals, resulting in a "metacarpal hand" deformity.[3,5] Third, radial digits, especially the thumb, are usually involved as demonstrated in our case series. This is likely related to the action of feeding sugarcane stems and retrieving its debris. Fourth, *Pseudomonas aeruginosa* and *Fusarium sacchari* wound infections are common due to contact with pesticides and agricultural produce.[4,6]

To reduce these injuries, we identified key contributing intrinsic and extrinsic factors, including defective equipment, inadequate protective gear and work-related factors, such as duration of repetitive work, poor concentration, carelessness and multitasking.[7] Bad luck and God's will were also frequently cited in a survey, suggesting lack of self-empowerment.[8] This may be unsurprising as these operators are often self-employed and received only basic education, making it difficult for them to overcome occupational hazards alone.[8,9] Furthermore, there is no minimum age required to operate the machine even though young workers are more likely to sustain occupational hand injuries due to inexperience.[4,10]

Therefore, a multipronged approach involving all stakeholders should be adopted. First, a regulatory committee should be established to ensure food vendors undergo and pass mandatory safety training before being allowed to operate the sugarcane juicer. This training should teach a uniform and correct operating procedure that allows users to safely set up, operate and shutdown the machine. Food handlers should also be educated and empowered to understand their personal responsibility in preventing workplace injuries, for example, by taking breaks at intervals and performing regular machine maintenance. Refresher courses should be readily offered. Second, the same task force should implement mandatory

directives, such as being of a minimum age to operate the machine, wearing personal protective equipment and placing warning signs and labels, to ensure that working conditions meet safety standards. Third, the governing body could also introduce safety guidelines to which the design of the sugarcane juicer must comply. For example, all rollers should be assembled in a horizontal orientation that allows sugarcane stems to be fed into the machine by gravity, instead of manual force. Fail-safe mechanisms, such as an automatic power-down if a jam is detected or the need to turn it off before cleaning and maintenance, must be fitted. The machine should also be designed with a safety covering over the rollers and a box-shaped fixture at the top to prevent the entire hand from entering the rollers. A device intercalated in the electric circuit to prevent reversal of rotation should be installed as well. Fourth, regular workplace inspections and risk assessments could be carried out by the regulatory committee to identify and address any machinery defects or unsafe workplace practices. These visits could also serve as avenues for food vendors to raise and address any safety concerns. Fifth, a registry of hand injuries sustained from the sugarcane juicer may be helpful to assess the effectiveness of the recommendations implemented by monitoring the incidence of injuries. The same registry can also be responsible for keeping track of near-miss accidents, which food operators can report through an open communication channel. This registry can even be expanded to include other common kitchen machinery such as food grinders, another common source of mutilating hand injuries not addressed in this article.

In conclusion, sugarcane juicer roller injuries lead to severe permanent disabilities due to intrinsic and extrinsic factors, such as machinery design, handler's inexperience and lack of an authority to oversee mandatory training and safety standards of machinery. To prevent costly loss of income and productivity to these individuals and society, these shortcomings should be addressed immediately.

Disclosure

The authors have no relevant financial or non-financial interests to disclose.

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Outcomes of nurse-led cryotherapy treatment for viral warts

Dear Editor,

Cryotherapy is a cost-effective treatment that can be performed by non-dermatologists for viral warts, which are very common.[1,2] The National University Hospital, Singapore runs a nurse-led wart clinic where nurses are trained to administer cryotherapy. This study reviewed eradication rates and side effects in patients treated at the nurse-led wart clinic.

A review of patients who attended the nurse-led wart clinic from 2015 to 2019 was performed. Patients with viral warts received their first cryotherapy session administered by a dermatologist. Subsequently, treatments were done at the nurse-led wart clinic. The standard treatment protocol consisted of paring, followed by cryotherapy with 2 freeze-thaw cycles. Lesions deemed by nurses to be eradicated would be confirmed by a dermatologist. Patients with ongoing treatment at the end of the study period or who had achieved eradication following the first dermatologist-administered treatment were excluded. Data on previous wart treatment, immunosuppression (conditions/therapies), number of cryotherapy sessions, treatment duration, and treatment postponement due to side effects were recorded.

Following the last cryotherapy session, we recorded the reasons for cessation of cryotherapy as follows: successful eradication, treatment failure, inability to commit to treatment frequency or inability to tolerate side effects. Recurrence was defined as new lesions being detected within 1 year from the last cryotherapy session. Treatment failure was defined as a recommendation by the dermatologist to pursue alternative treatment having deemed cryotherapy to be ineffective if continued. The recorded disposition for patients who ceased cryotherapy treatment were: given alternative treatment, or provided open-date appointment or referral to another hospital. Data was analysed using the 2-sample t-test and chi-square test.

A total of 703 patients were identified; 377 (53.6%) men, 326 (46.4%) women, 415 (59%) completed or remained on follow-up, and 288 (41%) defaulted follow-up. There were 166 (23.6%) patients who received previous treatment (cryotherapy, salicylic acid, Verrumal [Almirall Hermal, Reinbek, Germany], electrosurgery, or carbon dioxide lasers). There were 37 (5.3%) who were immunosuppressed, 12 (1.7%) had autoimmune disease, 18 (2.6%) were transplant recipients and 7 (1.0%) had active malignancy. Immunosuppressive therapies included prednisolone, azathioprine, mycophenolate mofetil, cyclosporin and chemotherapy.

Among patients who completed or remained on follow-up, 363 (87.5%) achieved eradication. Between cryotherapy sessions, 367 (88.4%) experienced no significant side effects, 12 (2.9%) experienced significant pain and 36 (8.7%) experienced blistering. There were 11 (2.7%) patients who required postponement of cryotherapy due to active blistering or unepithelised erosions. Among patients who achieved eradication, mean number of cryotherapy sessions was 5.82 (95% confidence interval [CI] 5.42–6.23) sessions, mean interval between sessions was 23.6 (95% CI 22.6–24.6) days and mean treatment duration was 144 (95% CI 132–156) days (Table 1). Among the 363 patients who

Table 1. Comparison of key outcomes.

Treatment outcomes	Completed follow-up				Defaulted follow-up	
	Total n=415	Eradication achieved n=363	Eradication not achieved n=52	*P* value	Total n=288	*P* value
Cryotherapy sessions, mean, no.	-	5.82	9.6	-	4.94	-
Interval between sessions, mean, days	23.4	23.6	25.2	0.424	22.7	0.198
Treatment duration, mean, days	-	144	233	-	124	-
Side effects, no.						0.546
Nil	367	321	46		255	
Pain	12	8	4		12	
Blistering	36	34	2		21	

achieved eradication, recurrence following eradication was seen in 20 (5.5%) patients of whom 12 (60%) had recurrence over the same body part; 20 (5.5%) were immunosuppressed.

Among the 52 patients who discontinued cryotherapy before achieving eradication, 30 (57.7%) met treatment failure, 18 (34.6%) were unable to commit to treatment frequency and 4 (7.7%) were unable to tolerate side effects. There were 45 (86.5%) patients who requested alternative treatment options, 6 (11.5%) requested for open-date appointments and 1 (1.9%) requested to be referred to another hospital. Mean number of cryotherapy sessions was 9.60 (95% CI 6.70–12.2), mean interval between sessions was 25.2 (95% CI 21.5–29.0) days and mean treatment duration was 233 (95% CI 172–295) days. Among the 52 patients, 5 (9.6%) patients were immunosuppressed. There was no statistical difference in session intervals between patients who achieved eradication and those who discontinued cryotherapy before achieving eradication (P=0.424).

Immunosuppressed patients were more likely to fail eradication (odds ratio 3.69, 95% CI 1.58–8.62, P=0.003). Among the 288 patients who defaulted treatment, the mean number of cryotherapy sessions was 4.94 (95% CI 4.58–5.31), mean interval between sessions was 22.7 (95% CI 21.3–24.1) days and mean treatment duration was 124 (95% CI 111–138) days. Between sessions, 255 (88.5%) experienced no significant side effects, 12 (4.2%) experienced pain and 21 (7.3%) experienced blistering. No data was available on reasons for default or discontinuation of therapy for these patients. Comparing patients who completed or remained on follow-up and patients who defaulted follow-up, there was no significant difference in the interval between sessions (P=0.198) and side-effect profiles (P=0.546).

Overall, eradication rate was good (87.5%) and frequency of side effects was acceptable (11.5%). Only a small proportion of patients (2.7%) required treatment postponement. Aggressive cryotherapy has been observed to be more effective though coupled with increased risk of side effects, which may be debilitating to some patients.[3-7] Balancing treatment effectiveness while minimising side effects is required to ensure patients ultimately benefit from treatment and can tolerate it. The low rate of treatment postponement indicates that our interval between treatment sessions (23.4 days) is appropriate, allowing adequate recovery while maintaining treatment effectiveness.[8] The mean duration required for eradication was 144 days, comprising about 6 sessions.

Patients who discontinued cryotherapy had received cryotherapy for a mean duration of 233 days, being treated for an additional 89 days before alternative treatment options were considered or effectiveness of cryotherapy was re-evaluated. Berth-Jones et al. noted that prolonging cryotherapy treatment did not necessarily increase the eradication rate.[9] To improve resource utilisation and cost savings, reviewing cryotherapy effectiveness around the 7th or 8th cryotherapy session (just beyond the mean duration required for eradication) can be done for consideration of alternative treatment. This may reduce unnecessary cryotherapy beyond the point when it would be considered ineffective.

No statistical differences in the interval between sessions or frequency of side effects were noted between patients who completed follow-up and those who defaulted follow-up to suggest treatment interval as a factor for the default rate (41%). Extrapolated reasons from patients who remained on follow-up but discontinued cryotherapy treatment include inability to commit and treatment frequency. Since multiple sessions are often required to achieve eradication, patient education through adequate counselling on the expected frequency and duration of cryotherapy treatment is important to help patients remain committed to treatment and for better resource utilisation.[10] Otherwise, alternative treatment modalities that require less time to achieve eradication can be offered.[11]

Nurse-administered cryotherapy remains effective and well tolerated. Dedicated and targeted treatment services or options may allow better streamlining of patients and consolidation of care. Outcomes can be improved by counselling patients on the expected treatment frequency and duration. An additional dermatologist review after a period of treatment when cryotherapy is expected to be successful may reduce unnecessary treatment extension. We suggest for all dermatological centres to upskill nurses to offer this service, which will provide dermatologists the time to manage more complex conditions.

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Evaluation on the adoption of eHealth App for electronic health record sharing system in Hong Kong

Dear Editor,

In Hong Kong, the eHealth App was launched in January 2021, as part of Stage Two development of the Electronic Health Record Sharing System. It provides the healthcare recipients, that is, those who have registered in the system, a series of functions to manage their health, such as accessing electronic health records and self-inputting health information.[1] We conducted a study to evaluate how the general population adopted the eHealth App and identify the contributing factors that may influence its adoption.

All healthcare recipients who authenticated the eHealth App and engaged with it before 31 December 2021 were included. Authentication was defined as successful following the user's login to the App using username and password. Descriptive analysis for the outcome variables was carried out and expressed as proportions. Adjusted odds ratio (AOR) with 95% confidence interval (CI) and *P* value were calculated to determine the strength of the correlation between facilitating factors and eHealth App usage. A *P* value of <0.05 was considered statistically significant.

A dataset consisting of 1,346,505 responses was analysed. Majority of respondents were aged 41–60 years (600,250 of 1,356,505; 44.6%). Number of female and male respondents were almost equally distributed (668,010 of 1,346,505; 49.61% versus 678,495 of 1,346,505; 50.39%). More respondents were healthy (937,798 of 1,346,505; 69.65%). Less than 1% of respondents were the "family member" who were taken care of by their family (5,366 of 1,346,505; 0.4%). A small group of respondents were caregivers (22,622 of 1,346,505; 1.68%) and less than 20% of respondents had joined government-subsidised health programmes (214,765, 15.95% vs 1,131,740 of 1,346,505; 84.05%).

Users were more likely to login if they were (1) aged 41–60 (AOR 6.43, 95% CI 6.15–6.72, *P*<0.001) or aged 60 years and over (AOR 11.90, 95% CI 11.07–12.79, *P*<0.001); (2) male (AOR 8.10, 95% CI 7.79–8.42, *P*<0.001); or (3) a caregiver (AOR 2329.67, 95% CI 1998.94–2715.11, *P*<0.001). Users with 2–3 chronic diseases (AOR 11.89, 95% CI 11.00–12.85, *P*<0.001) had the highest login frequency (Table 1).

Users were more likely to have input vital information for their own profile if they were: (1) older in age (41–60 years: AOR 4.82, 95% CI 4.56–5.09, *P*<0.001; over 60 years: AOR 5.07, 95% CI 4.74–5.43, *P*<0.001); (2) male (AOR 1.27, 95% CI 1.23–1.30, *P*<0.001); (3) had at least 1 chronic disease (1 chronic disease: AOR 2.63, 95% CI 2.55–2.72, *P*<0.001; 2–3 chronic diseases: AOR 3.76, 95% CI 3.62–3.91, *P*<0.001; >3 chronic diseases: AOR 3.59, 95% CI 3.01–4.27, *P*< 0.001); (4) a caregiver (AOR 2.55, 95% CI 2.36–2.76, *P*<0.001); and (5) a family member (AOR 1.86, 95% CI 1.65–2.10, *P*<0.001).

Users were more likely to update their personal profile if they were: (1) older in age (41–60 years: AOR 1.65, 95% CI 1.62–1.68, *P*<0.001; over 60 years:

Table 1. Factors associated with adoption of eHealth App.

	AOR (95% CI)	*P* value
Age (years)		
16–40	1 (ref)	
41–60	6.43 (6.15–6.72)	<0.001
>60	11.9 (11.07–12.79)	<0.001
Gender		
Male	8.10 (7.79–8.42)	<0.001
Female	1 (ref)	
Healthiness level[a]		
Healthy (no chronic disease)	1 (ref)	
Mild (1 chronic disease)	3.02 (2.88–3.17)	<0.001
Moderate (2–3 chronic diseases)	11.89 (11.00–12.85)	<0.001
Multiple (>3 chronic diseases)	8.30 (5.41–12.74)	<0.001
Family member		
Being a family member	0.88 (0.64–1.20)	0.427
Not being a family member	1 (ref)	
Caregiver		
Being a caregiver	2329 (1998.94–2715.11)	<0.001
Not being a caregiver	1 (ref)	
Joined government-subsidised health programmes		
No	1 (ref)	
Yes	0 (0–3.79E+06)	0.523

AOR: adjusted odds ratio; CI: confidence interval.
[a]Types of chronic illness included diabetes, hypertension, chronic kidney disease, coronary heart disease, respiratory disease, cancer.
P value of <0.05 was considered statistically significant.

AOR 1.48, 95% CI 1.43–1.52, *P*<0.001); (2) male (AOR 1.55, 95% CI 1.53–1.58, *P*<0.001); (3) had at least 1 chronic disease (1 chronic disease: AOR 1.06, 95% CI 1.05–1.08, *P*<0.001; 2–3 chronic diseases: AOR 1.21, 95% CI 1.18–1.25, *P*<0.001; >3 chronic diseases: AOR 1.33, 95% CI 1.17–1.51, *P*<0.0001); (4) a caregiver (AOR 3.21, 95% CI 3.09–3.34, *P*<0.001); or (5) a family member (AOR 2.54, 95% CI 2.37–2.72, *P*<0.001).

Users were more likely to manage consent sharing via the eHealth App if they were: (1) aged 41–60 years (AOR 1.06, 95% CI 1.00–1.11, *P*=0.048); (2) had at least 1 chronic disease (1 chronic disease: AOR 1.26, 95% CI 1.20–1.33, *P*<0.001; 2–3 chronic diseases: AOR 1.45, 95% CI 1.34–1.57, *P*<0.001; >3 chronic diseases: AOR 1.77, 95% CI 1.22–2.56, *P*<0.001); (3) a caregiver (AOR 3.51, 95% CI 3.18–3.87, *P*<0.001); and (4) a family member (AOR 2.86, 95% CI 2.42–3.38, *P*<0.001).

Users were more likely to download the COVID-19 Vaccine Pass QR code if they were: (1) male (AOR 1.19, 95% CI 1.18–1.20, *P*<0.001) and (2) a caregiver (AOR 1.23, 95% CI 1.19–1.27, *P*<0.001). Users were more likely to input vaccine records when they were (1) older (age 41–60 years: AOR 1.12, 95% CI 1.09–1.15, *P*<0.001; age >60: AOR 1.14, 95% CI 1.10–1.18, *P*<0.001); (2) a caregiver (AOR 1.92, 95% CI 1.82–2.03, *P*<0.001); or (3) a family member (AOR 1.54, 95% CI 1.38–1.71, *P*<0.001).

The elderly and individuals with more chronic diseases tended to use the eHealth App to manage their health records. The association between age and eHealth technology usage was inconsistent in past literature.[2] Some studies indicated that older adults were less likely to use the patient portal than younger adults,[2,3] while other studies discovered that the acceptance of eHealth among older users was positively affected by the perceived usefulness, ease of use, and quality of information.[2,4] Usage depends on the technological support provided, technology literacy and application's usability, such as information presented and system readability.[5,6] Greater use of the patient portal was associated with increased numbers of medical problems.[6-8] People could facilitate health management and improve health outcomes by using health applications.[9] eHealth technologies should be designed according to patients' needs and characteristics.[10]

The findings of this study provided insight into users' usage of the eHealth App. More support, such as download guides and tutorial videos, should be provided and tailored health messages could be included to enhance the adoption of eHealth App.

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