

Trends in fluid overload-related hospitalisations among patients with diabetes mellitus The impact of chronic kidney disease

Joshua Kuan Tan¹ MSc, Hanis Abdul Kadir¹ MSc, Gek Hsiang Lim¹ MSc, Julian Thumboo¹ FAMS, Yong Mong Bee² FRCP, Cynthia Ciwei Lim³ FRCP

ABSTRACT

Introduction: Fluid overload is a known complication in patients with diabetes mellitus, particularly those with cardiovascular and/or chronic kidney disease (CKD). This study investigates the impact of fluid overload on healthcare utilisation and its association with diabetes-related complications.

Method: Electronic medical records from the SingHealth Diabetes Registry (2013–2022) were analysed. Hospitalisations due to fluid overload were identified using International Classification of Diseases, 10th Revision (ICD-10) discharge codes. Trends were examined using Joinpoint regression, and associations were assessed with generalised estimating equation models.

Results: Over a period of 10 years, 259,607 individuals treated at primary care clinics and tertiary hospitals were studied. The incidence of fluid overload-related hospitalisations decreased from 2.99% (n=2778) in 2013 to 2.18% (n=2617) in 2017. However, this incidence increased from 2.42% (n=3091) in 2018 to 3.71% (n=5103) in 2022. The strongest associations for fluid overload-related hospitalisation were found with CKD stages G5 (odds ratio [OR] 6.61, 95% confidence interval [CI] 6.26–6.99), G4 (OR 5.55, 95% CI 5.26–5.86) and G3b (OR 3.18, 95% CI 3.02–3.35), as well as with ischaemic heart disease (OR 3.97, 95% CI 3.84–4.11), acute myocardial infarction (OR 3.07, 95% CI 2.97–3.18) and hypertension (OR 3.90, 95% CI 3.45–4.41). Additionally, the prevalence of stage G5 CKD among patients with fluid overload increased between 2018 and 2022.

Conclusion: Our study revealed a significant increase in fluid overload-related hospitalisations and extended lengths of stay, likely driven by severe CKD. This underscores an urgent need for initiatives aimed at slowing CKD progression and reducing fluid overload-related hospitalisations in diabetes patients.

Ann Acad Med Singap 2024;53:435-45

Keywords: chronic kidney disease, diabetes mellitus, fluid overload, healthcare utilisation, heart failure

CLINICAL IMPACT

What is New

- There has been an increasing trend in the number of patients with diabetes mellitus experiencing at least 1 hospital admission due to fluid overload within the SingHealth system in Singapore. This trend correlates with a growing healthcare burden.
- Our analysis indicates that the progression to end-stage chronic kidney disease (CKD) is a significant factor contributing to these trends.

Clinical Implications

- There is an urgent need for interventions to slow the progression of CKD and to reduce fluid overload-related hospitalisations among patients with diabetes mellitus.

INTRODUCTION

Diabetes mellitus (DM) is a major global health problem, contributing to significant clinical disease burden, healthcare expenditure and societal costs.¹ In Singapore, DM accounts for 2.9% of disability-adjusted life years and 4.3% of years lived with disability.^{2,3} By 2030, it is projected to cost approximately USD 1.89 billion in healthcare spending.⁴ The burden and costs of DM are expected to worsen due to the rising prevalence of diabetes-related macrovascular and microvascular complications, particularly cardiovascular disease (CVD) and chronic kidney disease (CKD).^{5,6} Furthermore, type 2 DM (T2DM) is a major risk factor for cardiorenal syndrome (CRS),⁷ a condition where CVD and CKD interact, leading to worsening dysfunction of both systems.⁸ Decompensated

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¹ Health Services Research Unit, Singapore General Hospital, Singapore

² Department of Endocrinology, Singapore General Hospital, Singapore

³ Department of Nephrology, Singapore General Hospital, Singapore

Correspondence: Dr Cynthia Ciwei Lim, Department of Renal Medicine, Singapore General Hospital, Academia Level 3, 20 College Road, Singapore 169856.

Email: cynthia.lim.c.w@singhealth.com.sg

CVD, CKD and CRS often present as symptomatic fluid overload and/or acute decompensated heart failure,⁹ necessitating hospitalisation.^{10–12} Severe fluid overload increases the risk of ventilatory support in the intensive care unit, prolonged hospitalisations, or recurrent hospitalisations,¹³ thus contributing significantly to morbidity, mortality and healthcare costs.

As CVD and CKD become more prevalent among individuals with DM,⁵ the occurrence of CRS and fluid overload is expected to lead to higher healthcare expenditure and productivity losses,¹⁴ a trend observed in the US.¹⁵ Between 2018 and 2021, we noted an increase in hospitalisations due to fluid overload among individuals with diabetes in Singapore.¹² However, the healthcare utilisation characteristics related to fluid overload in these patients have not been fully described. Fluid overload is a potentially avoidable and ambulatory-sensitive cause of unplanned hospitalisations. Understanding the trends and drivers of healthcare utilisation for fluid overload can inform targeted interventions and resource allocation to reduce hospitalisations and healthcare costs associated with diabetes. Therefore, we aimed to examine the long-term trends in hospitalisations due to fluid overload and explore the plausible reasons for these trends.

METHOD

Study design and population

We utilised data from the multi-institutional SingHealth Diabetes Registry (SDR), a comprehensive repository from the Singapore Health Services (SingHealth) Regional Health System in Singapore. We examined trends of fluid overload in the registry cohort from 2013 to 2022. The SDR includes data from electronic medical records and clinical databases, covering primary to tertiary care. It encompasses all individuals aged 18 and above diagnosed with DM, excluding those with pre-diabetes. Cases are annually identified using criteria that incorporate diagnosis codes (International Classification of Disease, 9th Revision [ICD-9] and 10th Revision [ICD-10]), prescription records and laboratory test records.¹⁶

Outcome ascertainment

Hospitalisations due to fluid overload were determined using ICD-10 diagnosis codes (E877, I50, I500, J81, N04 and R601) for fluid overload, heart failure, congestive heart failure, pulmonary oedema, nephrotic syndrome and generalised oedema, respectively. Fluid overload could be the principal cause of hospitalisation (coded

as primary discharge diagnosis) or could occur alongside another condition (coded as secondary discharge diagnosis). Thus, we analysed trends and associations for fluid overload both as the “principal diagnosis” (i.e. primary discharge diagnosis) and the “discharge diagnosis” (i.e. either the primary or secondary discharge diagnosis). To evaluate the healthcare burden attributable to fluid overload, we analysed the proportion of individuals who had 1 or more hospitalisations due to fluid overload each calendar year. We also examined the total number of hospitalisations caused by fluid overload and the total length of stay (LOS) for all fluid overload-related hospitalisations within a year. The total LOS was calculated as the sum of the LOS of all hospitalisations in a calendar year where fluid overload was either the principal or discharge diagnosis. The average LOS per patient with fluid overload was determined by dividing the total LOS by the number of patients with fluid overload-related hospitalisations.

Explanatory variables

A total of 17 sociodemographic and clinical variables related to diabetic complications were evaluated. These included age, sex, housing type (used as a surrogate measure of socioeconomic status), smoking status, mean HbA1c over 1 year, estimated glomerular filtration rate (eGFR) category, hypertension, hyperlipidaemia, and diabetes-related macrovascular and microvascular diseases. The macrovascular diseases included ischaemic heart disease (IHD), peripheral arterial disease, stroke (both ischaemic and haemorrhagic). The microvascular diseases included lower extremity amputation (both major and minor), diabetes-related eye complications, and diabetic foot complications. eGFR was calculated using the last serum creatinine value of the calendar year and the CKD EPI 2021 equation.¹⁷ eGFR categories were aligned with the Kidney Disease: Improving Global Outcomes (KDIGO) nomenclature.¹⁸ The criteria for ascertaining these macrovascular and microvascular diseases have been described previously.⁵

Statistical analyses

The analysis was conducted for 4 age bands; 18–44 years (age band 1), 45–64 years (age band 2), 65–74 years (age band 3), and 75 years and older (age band 4) to control for age effects on trend estimates. When calculating event rates, the denominator included all patients present in the registry each year, while the numerator consisted of those who experienced the outcome. Patients who died but experienced specific outcomes

within their year of death were included in the analysis for that year but excluded from the registry in subsequent years. Joinpoint regression methodology¹⁹ was used to analyse trends in the event rates of fluid overload hospitalisations, allowing a maximum of 1 Joinpoint based on the 10 years of observations. Generalised estimating equation (GEE) models were employed to evaluate the associations between fluid overload and explanatory variables. Multivariable GEE regression models were constructed to assess the association between explanatory variables and the occurrence of fluid overload-related hospitalisation, the number of such hospitalisations, and the LOS for these hospitalisations. The covariables were determined a priori, including all 17 sociodemographic and clinical variables in the multivariable GEE regression models. We used the binomial family with a logit link for the occurrence of at least 1 fluid overload-related hospitalisation (a binary outcome) within the calendar year, and Poisson family with a log link for the number of hospitalisations for fluid overload or total LOS. All GEE models included the calendar year as an independent variable and were adjusted for the confounding effect of age. Additional descriptive analyses were performed on variables identified by the GEE models as having the strongest associations. All analysis were performed using Stata version 14.0 (StataCorp, College Station, TX, US) or Joinpoint Regression Program version 5.02 (Statistical Methodology and Applications Branch, Surveillance Research Programme, National Cancer Institute, US). The study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist (Supplementary Table S1).

Ethics approval

The SingHealth Centralised Institutional Review Board (CIRB) determined that an ethics review was not required for the use of de-identified data obtained during routine clinical care (SingHealth CIRB reference number: 2022/2133). Since all participant data were de-identified, a waiver for participant consent was also granted.

RESULTS

This study included 259,607 unique patients. The characteristics of the registry are detailed in Table S2. Throughout the study period, the sex and ethnicity of the registry closely mirrored that of the Singapore population.²⁰ In 2022, nearly all patients in the registry (98.78%) had T2DM, with a small proportion (<1%) having type 1 or other types of diabetes (e.g. drug-induced, gestational,

monogenic and secondary diabetes). The SDR is a dynamic cohort, and movement of the population in and out of the registry is illustrated in Fig. S1.

Trends in fluid overload

Over the study period, we observed an increase in the proportion of patients in the registry admitted for fluid overload (Table 1). In 2013, 0.94% of the registry (n=877) had at least 1 hospitalisation where fluid overload was the principal diagnosis. This prevalence decreased to 0.67% in 2017 but then sharply increased to 1.34% (n=1849) in 2022. A similar trend was seen for fluid overload as a discharge diagnosis, where the prevalence decreased from 2.99% (n=2778) in 2013 to 2.18% (n=2618) in 2017 and increased to 3.71% (n=5103) in 2022. The total LOS for all patients with fluid overload, whether as the principal diagnosis or discharge diagnosis, also increased over the study period. After adjusting for the number of patients with fluid overload in the registry, it was found that the average LOS per patient increased over time, indicating that patients spent longer durations in the hospital in the later years of the study.

Fig. 1 and Table S3 demonstrate that older adults in age bands 3 and 4 experienced event rates of at least 1 fluid overload-related hospitalisation that were 2 to 5 times higher than those of younger adults in age band 1. Additionally, Fig. 1 shows that older adults in age band 4 exhibited the steepest increase in the rates of fluid overload-related hospitalisation for both principal and discharge diagnoses.

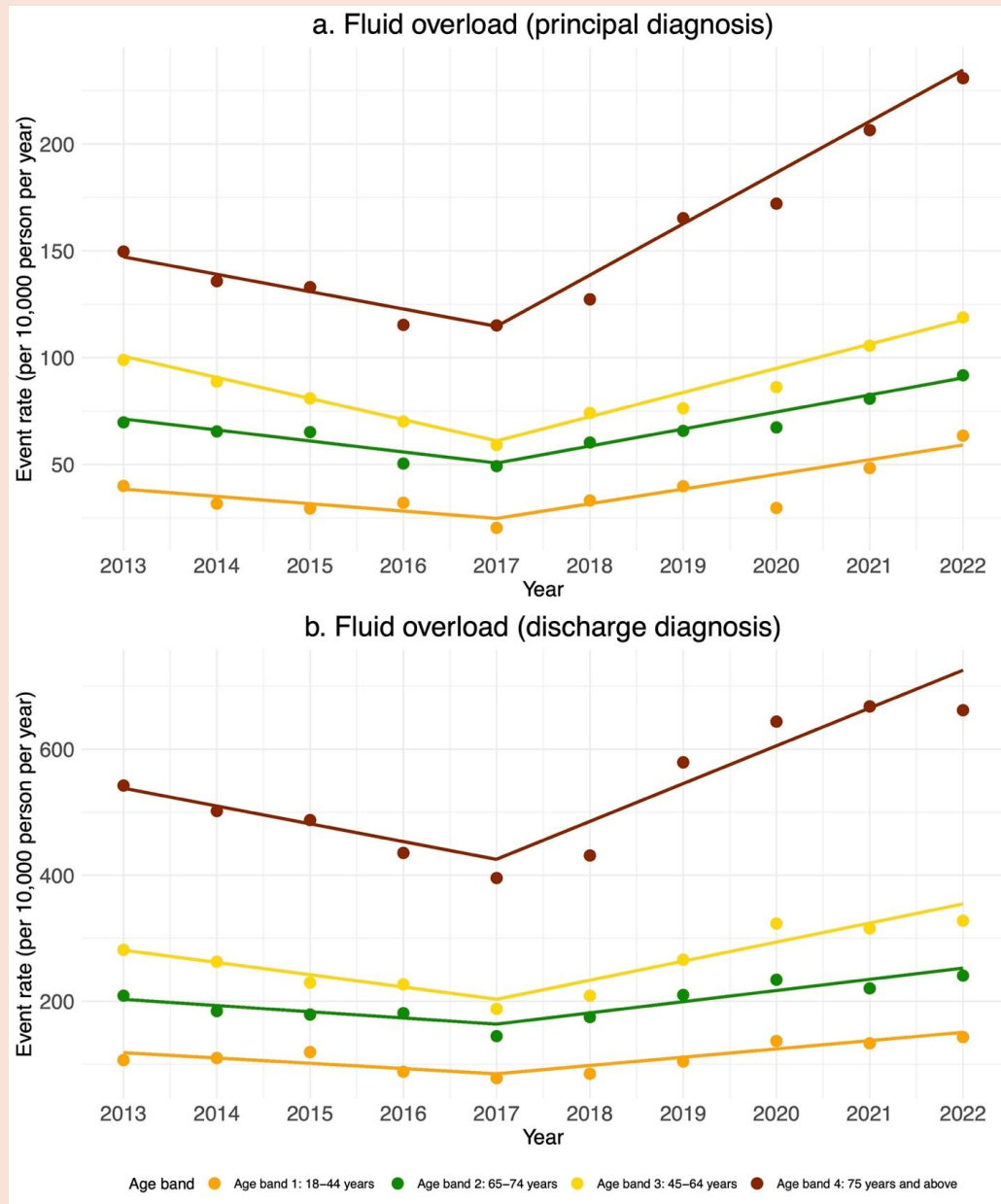
Joinpoint regression (Fig. 1) revealed that there was a statistically significant change in trends for fluid overload across all age bands, for both principal and discharge diagnoses. There was an initial decline from 2013 to 2017, followed by an increase from 2017 to 2022. Table S3 shows that in all Joinpoint models indicated a positive and statistically significant annual percentage change (APC) for the segments from 2017 to 2022. In age band 4, the APC was 15.39% (95% confidence interval [CI] 12.39%, 20.37%) for fluid overload as the principal diagnosis and 11.26% (95% CI 6.39%, 24.81%) for fluid overload as the discharge diagnosis. The dynamic nature of the SDR cohort (Fig. S1) added complexity to the analysis of fluid overload hospitalisation trends. To address this, we examined the flow of patients with fluid overload. Fig. S2 showed the trends in the annual inflow of patients. Between 2013 and 2017, there was a decrease in the absolute number of new patients admitted for fluid overload, while the number of patients with fluid overload already

Table 1. Utilisation characteristics of patients with fluid overload-related hospitalisations.

Year	Fluid overload as principal diagnosis					Fluid overload as discharge diagnosis				
	SDR population	SDR year-on-year growth rate (%)	No. of patients (% of registry)	Unadjusted year-on-year growth rate (%)	Total LOS (days)	Average LOS per patient (days)	No. of patients (% of registry)	Unadjusted year-on-year growth rate (%)	Total LOS (days)	Average LOS per patient (days)
2013	92,990	-	877 (0.94)	-	7820	8.92	2778 (2.99)	-	41,544	14.95
2014	96,846	4.15	839 (0.87)	-4.33	7577	9.03	2678 (2.77)	-3.60	41,616	15.54
2015	105,181	8.61	882 (0.84)	5.13	7338	8.32	2771 (2.63)	3.47	40,366	14.57
2016	111,963	6.45	792 (0.71)	-10.20	5828	7.36	2802 (2.50)	1.12	41,159	14.69
2017	120,221	7.38	810 (0.67)	2.27	6408	7.91	2617 (2.18)	-6.60	35,319	13.50
2018	127,989	6.46	1011 (0.79)	24.81	8302	8.21	3091 (2.42)	18.11	43,191	13.97
2019	134,670	5.22	1236 (0.92)	22.26	9939	8.04	4194 (3.11)	35.68	62,298	14.85
2020	140,859	4.60	1356 (0.96)	9.71	13,035	9.61	5008 (3.56)	19.41	78,597	15.69
2021	137,584	-2.33	1610 (1.17)	18.73	16,288	10.12	4868 (3.54)	-2.80	78,914	16.21
2022	137,627	0.03	1849 (1.34)	14.84	19,977	10.80	5103 (3.71)	4.83	83,471	16.36

LOS: length of stay; SDR: SingHealth Diabetes Registry

Fig. 1. Trends in fluid overload-related hospitalisations by age bands.



included in the previous year's registry remained relatively constant. Starting in 2018, there was a rise in the number of newly diagnosed patients with fluid overload, including both new entrants to the SDR and those already present in the SDR from the previous year, across both principal and discharge diagnosis categories.

Variables associated with fluid overload-related hospitalisations

Patients with stages G3b–G5 CKD, hypertension, IHD and acute myocardial infarction (AMI) had the highest odds of experiencing at least one hospitalisation for fluid overload, whether as the principal or the discharge diagnosis, throughout

the study period (Table 2). These associations remained consistent when analysed using individual logistic regression models for each year (data not shown). Similarly, these factors were also most strongly associated with the number of fluid overload-related hospitalisations and total LOS.

Detailed trends in CKD and IHD

Given the strong association between CKD and IHD with fluid overload-related hospitalisations (Table 2), we further examined the trends in these variables in Figs. 2 and 3 and Table S4. Fig. 2 shows an increase in the proportion of stage G5 CKD between 2018 and 2022 among those with fluid overload-related hospitalisations (Figs. 2b and 2c),

with the most significant increase observed when fluid overload was the principal diagnosis (Fig. 2b). This trend was evident among patients newly added to the SDR each year (Figs. 3a and 3b) as well as those already present in the previous year's registry (Figs. 3c and 3d). Conversely, the proportions of CKD stages 3B, 4 and 5 remained unchanged over the years among the entire SDR population (Fig. 2a) and those without fluid overload-related hospitalisations (Figs. 2d and 2e).

We observed a gradual increase in the prevalence of IHD in the entire SDR cohort (Fig. S3a, Table S5), consistent with our earlier study.⁵ Interestingly, there was no significant change in the prevalence of IHD among patients with fluid overload, whether as the principal or discharge diagnosis (Figs. S3b and S3c, Fig. S4).

DISCUSSION

In this study, we observed a rising rate of fluid overload-related hospitalisations among individuals with diabetes over the past decade. This increase was accompanied by a growing healthcare burden attributable to fluid overload, as evidenced by a rise in total inpatient bed days and average LOS. We found that stages G3b–G5 CKD, IHD, AMI and hypertension were most strongly associated with fluid overload, both as principal and discharge diagnoses. Furthermore, the prevalence of stage G5 CKD among patients with fluid overload had increased alongside the rise in fluid overload-related hospitalisations over the past five years. This study offers valuable insight into the epidemiology of fluid overload-related hospitalisations among individuals with DM. Joinpoint analysis revealed a decline in fluid overload rates from 2013 to 2017, followed by a significant increase from 2018 to 2022. The inflection point in 2017 across all Joinpoint models may be attributed to extrinsic factors. Notably, that year, the Ministry of Health restructured the public healthcare system, transferring two polyclinics previously managed by SingHealth to other healthcare clusters.²¹ Consequently, we observed a significant outflow of more than 20,000 patients from the SDR in 2017 (Fig. S1). These patients may have sought care with other healthcare clusters if they experienced fluid overload. However, these changes cannot fully explain the sustained increase in fluid overload-related hospitalisations and LOS between 2018 and 2022.

Our analysis suggests that the changes in the prevalence of fluid overload-related hospitalisations may be attributed to the progression of CKD. Utilising GEE models, we found that stages G3b–G5 CKD, IHD, AMI and hypertension are

associated with fluid overload, both as principal and discharge diagnoses. These associations remained strong in GEE models for the number of hospitalisations and LOS (Table 2). This indicates that G3b–G5 CKD, IHD, AMI and hypertension are linked not only to fluid overload but also to the increasing healthcare burden resulting from it. From 2013 to 2016, we observed an initial decline in the proportion of patients with stage G5 CKD, both with and without fluid overload (for both principal and discharge diagnoses; Figs. 2a, 2b and 2c, Table S4). This suggests that the initial decline in fluid overload may be partially due to the reduced number of patients with advanced CKD during the earlier years of the study. However, from 2018 to 2022, there was an increasing proportion of patients with stage G5 CKD, both with and without fluid overload (for both principal and discharge diagnoses) between 2018 and 2022 (Figs. 2a, 2b and 2c, Table S4), which aligns with the increasing trend in fluid overload-related hospitalisations (Fig. 1). This suggests that the progression to stage G5 CKD may be a significant driving factor.

This observation may also explain the sharp increase in fluid overload-related hospitalisations and LOS in older adults. In this population, the combination of diabetes, hypertension and obesity heightens the risk of CKD, IHD and possibly CRS. However, studying CRS is technically challenging because clinical codes for CRS and its four subtypes have not yet been defined. Additionally, creating and interpreting interaction terms between CRS, CKD and IHD in a GEE model can be complex. Future research could aim to model these interactions through causal modelling approaches. The increasing proportion of patients with stage G5 CKD and fluid overload within the existing SDR cohort (Figs. 3c and 3d) is worrisome. Despite evidence that guideline-directed medical therapy (GDMT) can slow CKD progression,²² our findings suggest that the benefits of GDMT are not yet fully realised at the population level, possibly due to delays in its uptake.¹² Factors contributing to this delay include clinical inertia among patients and physicians,²³ low awareness of CKD among patients, multimorbidity, fragmented CKD care, and high drug prices.²⁴ Therefore, we welcome recent efforts to promote adherence to GDMT, including clinical practice guidelines by the Singapore Agency for Care Effectiveness²⁵ and drug subsidies.

Interestingly, the number of new SDR patients who experienced fluid overload-related hospitalisations and stage G5 CKD also increased (Figs. 3a, 3b and Table S4). This suggests that more patients who are not previously engaged with SingHealth's

Table 2. Factors associated with (a) any hospitalisation for fluid overload, (b) number of hospitalisations for fluid overload and (c) total length of stay for fluid overload hospitalisation, as principal and discharge diagnoses.

Variables	(a) Any hospitalisation for fluid overload				(b) No. of hospitalisations for fluid overload				(c) Total length of stay for fluid overload			
	Principal diagnosis		Discharge diagnosis		Principal diagnosis		Discharge diagnosis		Principal diagnosis		Discharge diagnosis	
	OR† (95% CI)	P value	OR† (95% CI)	P value	IRR‡ (95% CI)	P value	IRR‡ (95% CI)	P value	IRR‡ (95% CI)	P value	IRR‡ (95% CI)	P value
Female	Reference		Reference		Reference		Reference		Reference		Reference	
Male	0.96 (0.91–1.01)	0.118	0.85 (0.82–0.87)	<0.001	1.01 (0.97–1.06)	0.61	0.9 (0.88–0.92)	<0.001	0.86 (0.85–0.87)	<0.001	0.89 (0.88–0.91)	<0.001
Age (per year increase)	1.00 (1.00–1.00)	0.075	1.01 (1.01–1.02)	<0.001	1.00 (1.00–1.00)	0.041	1.01 (1.01–1.01)	<0.001	1.01 (1.01–1.01)	<0.001	1.00 (1.00–1.00)	<0.001
Housing type	Reference		Reference		Reference		Reference		Reference		Reference	
1- and 2-room flat	Reference		Reference		Reference		Reference		Reference		Reference	
3-room flat	0.73 (0.68–0.79)	<0.001	0.79 (0.75–0.83)	<0.001	0.64 (0.60–0.68)	<0.001	0.75 (0.72–0.77)	<0.001	0.85 (0.84–0.86)	<0.001	0.71 (0.70–0.73)	<0.001
4-room flat	0.68 (0.63–0.74)	<0.001	0.77 (0.73–0.80)	<0.001	0.61 (0.58–0.65)	<0.001	0.73 (0.70–0.76)	<0.001	0.79 (0.78–0.80)	<0.001	0.65 (0.64–0.67)	<0.001
5-room and executive flats	0.63 (0.58–0.68)	<0.001	0.71 (0.67–0.75)	<0.001	0.56 (0.53–0.60)	<0.001	0.68 (0.65–0.70)	<0.001	0.75 (0.74–0.76)	<0.001	0.61 (0.60–0.63)	<0.001
Condominium (Private)	0.48 (0.42–0.55)	<0.001	0.52 (0.48–0.57)	<0.001	0.42 (0.38–0.48)	<0.001	0.50 (0.47–0.54)	<0.001	0.52 (0.51–0.53)	<0.001	0.42 (0.40–0.44)	<0.001
Landed house (Private)	0.61 (0.54–0.70)	<0.001	0.63 (0.58–0.69)	<0.001	0.52 (0.47–0.58)	<0.001	0.59 (0.55–0.63)	<0.001	0.68 (0.66–0.69)	<0.001	0.58 (0.56–0.61)	<0.001
Smoking status	Reference		Reference		Reference		Reference		Reference		Reference	
Non-smoker	Reference		Reference		Reference		Reference		Reference		Reference	
Ex-smoker	1.85 (1.69–2.03)	<0.001	1.97 (1.85–2.09)	<0.001	1.58 (1.47–1.70)	<0.001	1.55 (1.48–1.61)	<0.001	1.73 (1.70–1.75)	<0.001	1.97 (1.92–2.03)	<0.001
Active smoker	1.32 (1.21–1.43)	<0.001	1.41 (1.34–1.48)	<0.001	1.25 (1.17–1.34)	<0.001	1.30 (1.25–1.35)	<0.001	1.20 (1.18–1.21)	<0.001	1.26 (1.22–1.29)	<0.001
Unknown	0.75 (0.71–0.79)	<0.001	0.87 (0.85–0.90)	<0.001	0.77 (0.74–0.80)	<0.001	0.78 (0.76–0.79)	<0.001	1.02 (1.01–1.03)	<0.001	0.86 (0.84–0.87)	<0.001
Comorbidities and complications	Reference		Reference		Reference		Reference		Reference		Reference	
Mean Hba1c (per 1% increase)	0.96 (0.94–0.97)	<0.001	0.96 (0.95–0.97)	<0.001	0.95 (0.93–0.96)	<0.001	0.95 (0.94–0.95)	<0.001	0.93 (0.93–0.93)	<0.001	0.91 (0.91–0.92)	<0.001
Hypertension	6.16 (4.67–8.12)	<0.001	3.90 (3.45–4.41)	<0.001	6.77 (5.26–8.71)	<0.001	4.03 (3.62–4.50)	<0.001	3.57 (3.47–3.68)	<0.001	10.67 (9.43–12.06)	<0.001
Hypercholesterolaemia	0.73 (0.63–0.84)	<0.001	0.68 (0.63–0.74)	<0.001	0.72 (0.64–0.82)	<0.001	0.73 (0.68–0.78)	<0.001	0.53 (0.53–0.54)	<0.001	0.63 (0.60–0.65)	<0.001

Table 2. Factors associated with (a) any hospitalisation for fluid overload, (b) number of hospitalisations for fluid overload and (c) total length of stay for fluid overload hospitalisation, as principal and discharge diagnoses. (Cont'd)

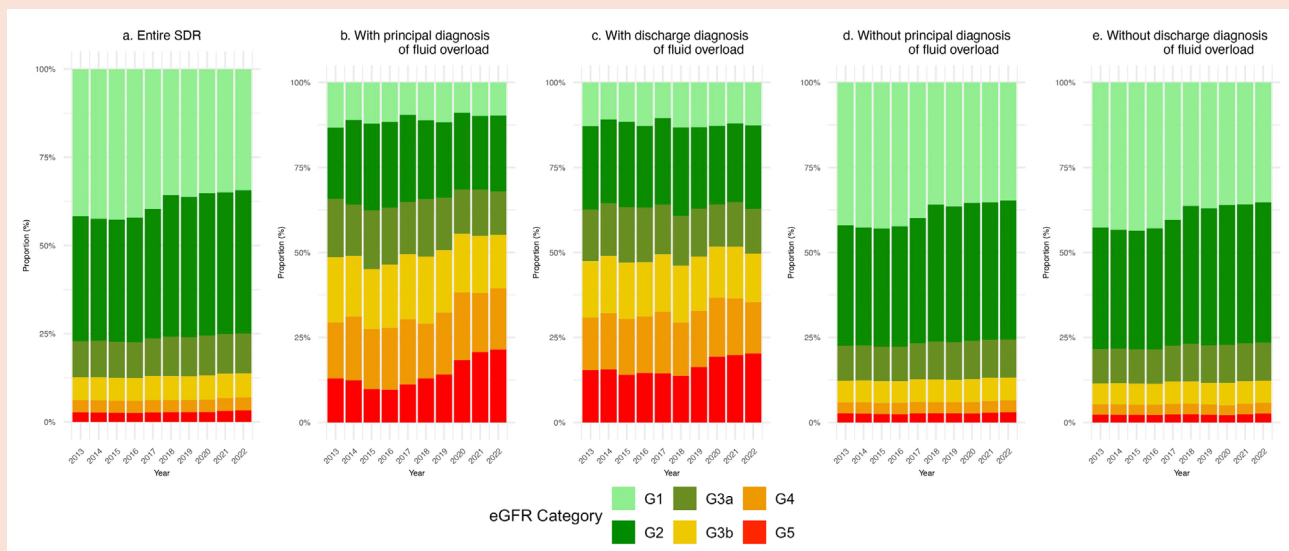
Variables	(a) Any hospitalisation for fluid overload				(b) No. of hospitalisations for fluid overload				(c) Total length of stay for fluid overload			
	Principal diagnosis		Discharge diagnosis		Principal diagnosis		Discharge diagnosis		Principal diagnosis		Discharge diagnosis	
	OR ^a (95% CI)	P value	OR ^a (95% CI)	P value	IRR ^b (95% CI)	P value	IRR ^b (95% CI)	P value	IRR ^b (95% CI)	P value	IRR ^b (95% CI)	P value
IHD	4.79 (4.52–5.07)	<0.001	3.97 (3.84–4.11)	<0.001	5.33 (5.06–5.60)	<0.001	4.27 (4.15–4.39)	<0.001	3.50 (3.47–3.53)	<0.001	5.08 (4.98–5.17)	<0.001
AMI	1.81 (1.71–1.91)	<0.001	3.07 (2.97–3.18)	<0.001	1.74 (1.66–1.82)	<0.001	2.39 (2.33–2.45)	<0.001	2.94 (2.91–2.96)	<0.001	1.82 (1.79–1.85)	<0.001
Peripheral arterial disease	1.41 (1.31–1.51)	<0.001	1.58 (1.52–1.66)	<0.001	1.46 (1.38–1.54)	<0.001	1.58 (1.54–1.63)	<0.001	2.04 (2.02–2.06)	<0.001	1.70 (1.67–1.74)	<0.001
Ischaemic stroke	0.96 (0.90–1.02)	0.184	1.21 (1.16–1.25)	<0.001	0.99 (0.94–1.05)	0.736	1.18 (1.14–1.21)	<0.001	1.46 (1.45–1.47)	<0.001	1.08 (1.06–1.10)	<0.001
Haemorrhagic stroke	1.05 (0.90–1.22)	0.536	1.41 (1.30–1.53)	<0.001	1.15 (1.02–1.30)	0.02	1.34 (1.27–1.42)	<0.001	1.86 (1.84–1.89)	<0.001	1.17 (1.12–1.22)	<0.001
Lower extremity amputation (major)	1.00 (0.79–1.25)	0.968	1.88 (1.63–2.15)	<0.001	0.89 (0.75–1.06)	0.187	1.23 (1.14–1.33)	<0.001	2.37 (2.34–2.41)	<0.001	1.03 (0.97–1.09)	0.372
Lower extremity amputation (minor)	0.96 (0.81–1.15)	0.67	1.25 (1.12–1.39)	<0.001	0.91 (0.79–1.05)	0.197	1.05 (0.98–1.13)	0.137	1.67 (1.65–1.70)	<0.001	1.18 (1.13–1.23)	<0.001
Diabetic foot and peripheral angiopathy	0.92 (0.87–0.97)	0.002	0.88 (0.85–0.91)	<0.001	0.95 (0.91–0.99)	0.018	1.04 (1.02–1.07)	<0.001	0.87 (0.87–0.88)	<0.001	0.78 (0.77–0.79)	<0.001
Diabetic eye disease	0.78 (0.74–0.82)	<0.001	0.81 (0.78–0.83)	<0.001	0.82 (0.79–0.86)	<0.001	0.86 (0.84–0.88)	<0.001	0.88 (0.87–0.88)	<0.001	0.90 (0.88–0.91)	<0.001
CKD stage												
Stage G1	Reference		Reference		Reference		Reference		Reference		Reference	
Stage G2	1.46 (1.35–1.58)	<0.001	1.27 (1.21–1.32)	<0.001	1.44 (1.35–1.54)	<0.001	1.34 (1.30–1.39)	<0.001	1.08 (1.07–1.09)	<0.001	1.38 (1.35–1.42)	<0.001
Stage G3a	2.59 (2.37–2.83)	<0.001	1.98 (1.88–2.09)	<0.001	2.59 (2.41–2.80)	<0.001	2.15 (2.06–2.24)	<0.001	1.66 (1.64–1.68)	<0.001	2.61 (2.53–2.68)	<0.001
Stage G3b	4.40 (4.02–4.81)	<0.001	3.18 (3.02–3.35)	<0.001	4.47 (4.15–4.81)	<0.001	3.28 (3.15–3.42)	<0.001	2.58 (2.55–2.62)	<0.001	4.74 (4.61–4.88)	<0.001
Stage G4	7.17 (6.55–7.85)	<0.001	5.55 (5.26–5.86)	<0.001	6.65 (6.17–7.17)	<0.001	4.84 (4.65–5.05)	<0.001	4.12 (4.07–4.17)	<0.001	7.98 (7.75–8.21)	<0.001
Stage G5	6.48 (5.90–7.13)	<0.001	6.61 (6.26–6.99)	<0.001	5.48 (5.06–5.93)	<0.001	4.91 (4.71–5.13)	<0.001	4.00 (3.95–4.05)	<0.001	5.93 (5.75–6.11)	<0.001

^a Odds ratio

^b Incidence rate ratio

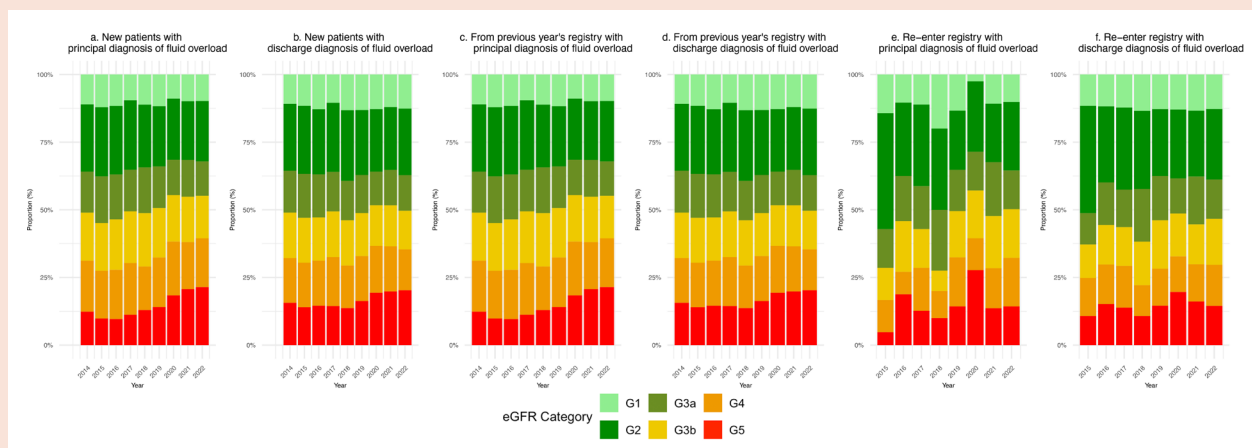
AMI: acute myocardial infarction; CI: confidence interval; CKD: chronic kidney disease; IHD: ischaemic heart disease; IRR: incidence rate ratio; OR: odds ratio

Fig. 2. Characteristics of eGFR-defined CKD status among different subgroups of patients in the SingHealth Diabetes Registry (SDR).



CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate

Fig. 3. Characteristics of eGFR-defined CKD status among patients with fluid overload: (a) and (b) refer to new patients in the registry who were not in the registry in the previous calendar year; (c) and (d) refer to existing patients in the registry; and (e) and (f) refer to patients who had left the registry in the preceding calendar years then re-entered in that calendar year.



CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate

healthcare system were entering the SDR with late-stage CKD and in fluid overload in recent years. These individuals may have been receiving care at other healthcare settings before entering the SingHealth care system late in their CKD progression, or they may not have been diagnosed with CKD or receiving regular follow-up care. In both instances, our results highlight the urgent need for national-level programmes to identify individuals with CKD, ensure continuity of care across all healthcare settings, and facilitate advance care planning in anticipation of progression to kidney failure.²⁶ In this study, we conducted an extensive longitudinal analysis of fluid overload

trends among a multiethnic cohort of individuals with diabetes. Our detailed analysis supports the Lancet Commission's call to action to improve diabetes care by identifying populations at risk of adverse health outcomes.²⁷ It offers valuable insights for public health interventions and future research as Singapore grapples with a rapidly ageing population. Based on these results, our hospital system is planning to implement or expand population health programmes to reduce fluid overload-related hospitalisations and slow the progression of CKD.²⁸ The issues identified by this study may also apply to other healthcare systems with ageing or super-ageing populations.

The limitations of our study arise from the dynamic nature of the SDR, particularly patients who exit the registry to seek clinical care at other healthcare institutions. The absence of data on fluid overload outcomes from other healthcare clusters or the private sector could influence our results. However, since the SingHealth cluster is the largest of the healthcare clusters in Singapore, the observed trends are likely similar in other clusters. Additionally, there may be bias related to outcome ascertainment as we used discharge codes that may be influenced by physician documentation and clinical coding practices. To minimise the bias, we considered fluid overload as both principal and discharge diagnoses and used a range of ICD codes (Table S6) to identify patients experiencing fluid overload in the context of DM and kidney disease, including those with unrecognised heart failure with preserved ejection fraction, which might not be included in studies focusing solely on heart failure.^{29,30} Furthermore, while we analysed sociodemographic and clinical factors as potential explanatory variables, other drivers for the outcomes, such as socioeconomic determinants of health (e.g. personal income and educational level) and comorbidities (e.g. frailty and infection), were not included in this analysis. Interactions between the variables were not explored and should be considered in future analyses. Finally, our results may not be generalisable to other healthcare settings where the prevalence and risks of CKD and IHD differ.

CONCLUSION

This study highlighted an increasing occurrence of fluid overload-related hospitalisations within a significant and representative subsection of the Singapore population. Alarming, our findings suggest that the rising rates of fluid overload may indicate an impending surge in kidney failure cases across Singapore, with direct implications for healthcare utilisation. There is an urgent need for efforts to slow the progression of CKD and reduce fluid overload-related hospitalisations.

Supplementary materials

Table S1. STROBE Statement: Checklist of items for the reporting of observational studies.

Table S2. Population structure, demographics and comorbidities of the SDR population from 2013 to 2022.

Table S3. Event rates for fluid overload by age bands.

Table S4. Characteristics of patients by eGFR category and year.

Table S5. Characteristics of patients by IHD status and year.

Table S6. Counts and relative frequencies of ICD-10 codes used for outcome ascertainment.

Fig. S1. Progression of patients through the SDR from 2013 to 2022.

Fig. S2. Stock and flow diagram for patients with fluid overload in the SDR.

Fig. S3. Characteristic of IHD status among different subgroups of patients in the SDR.

Fig. S4. Characteristics of IHD status among patients with fluid overload.

Acknowledgement

The authors would like to thank Ms Xin Xiaohui from the Health Services Research Unit, Singapore General Hospital, for her support in the project.

Declaration

All authors declare no relevant conflict of interest and no financial interest in this manuscript.

Ethics statement

SingHealth Centralised Institutional Review Board (2022/2133) approved the use of de-identified data and waiver of patient informed consent for this project.

Data availability statement

Data sharing is available and subjected to institutional data-sharing policies. Further enquiries can be directed to the corresponding author.

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