Genetics in Medicine Open (2024) 2, 101876

ELSEVIER

Genetics in Medicine OPEN
An Official Journal of the ACMG

www.journals.elsevier.com/genetics-in-medicine-open

ARTICLE

Genetic kidney disease has a higher likelihood and cost of inpatient admissions compared to other aetiologies

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ARTICLE INFO

Article history:
Received 4 July 2023
Received in revised form
14 July 2024
Accepted 17 July 2024
Available online 25 July 2024

Keywords:
Chronic kidney disease
Genetic kidney disease
Health economics
Health service utilization

ABSTRACT

Purpose: There is increasing recognition of monogenic aetiologies for kidney disease. We sought to identify whether genetic kidney disease (GKD) has distinct hospitalization patterns compared to other forms of chronic kidney disease (CKD).

Methods: Health service utilization analysis was undertaken in a CKD cohort study across public hospital services in Queensland, Australia. CKD due to clinically coded potential monogenic causes was compared to all other causes in terms of annual frequency, cost, and type of hospital admission.

Results: We analyzed 7 years of hospital admissions data (809,188 admissions) among 29,046 patients. Compared to non-genetic CKD, GKD was associated with a higher likelihood and cost of admissions. GKD had consistently more admissions (mean excess annual number of admissions increasing from 5.2 in year 1 to 13.4 in year 7) and more costly admissions (mean excess annual cost increasing from $5,265 in year 1 to $12,993 in year 7). This gap in hospitalization likelihood and cost increased over time for both surgical and medical admission episodes, but not for all (immunological, cancer) causes of admissions.

Conclusion: Understanding the nature and extent of differences in healthcare needs between GKD and other CKD will enable better secondary prevention and inform resource allocation decisions to reduce healthcare system pressures attributable to knowable causes.

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Article Publishing Charge (APC) for this article was paid by Andrew J. Mallett.

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doi: https://doi.org/10.1016/j.gimo.2024.101876

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Introduction

Chronic kidney disease (CKD) affects 1 in 7 Australian adults.[1] It is associated with the personal burden of disease and excess healthcare service utilization.[2] For some, the final disease stage of kidney failure will be reached, involving resource-intensive kidney replacement therapy. Hemodialysis represents 1.4 million inpatient episodes annually, or 13% of all hospitalizations in Australia,[3] and has an incidence of approximately 120 new patients per million population annually.[4] Even modest reductions of CKD progression and mitigation of its impacts are likely to have strong implications for healthcare system resources,[5] human well-being, and productivity.[6]

Through concerted efforts to collate and synthesize outcomes of clinical research, there are multiple established clinical guidelines for CKD, ranging from blood pressure,[7] lipid[8] and bone disease management,[9] to nomenclature,[10] types of kidney disease,[11–13] and specific aetiologies.[14,15] In addition to these evidence-based management approaches, new efforts toward addressing the health and cost burdens of CKD are emerging. Primary renal diagnosis potentially provides predictive or prognostic information to guide clinical management. Distinct aetiologies of CKD have been associated with differential health outcomes, including age of onset, acuity, contributing or consequent comorbidities, disease progression, and disease-modifying therapies. Further, differing primary renal diagnoses have also been linked to distinctive healthcare utilization outcomes, with diabetic nephropathy associated with higher odds of high-cost hospital care use than renovascular disease and glomerulonephritis.[16]

Genetic kidney disease (GKD) represents a broad spectrum of monogenic disorders affecting approximately 10% of adults with CKD.[17,18] While previously directed therapies were not available for many GKDs, this is changing.[19–21] The approach to clinical diagnosis is also changing with the implementation of diagnostic genetic testing[22,23] which has proven validity[24] and strong support from specialist clinicians.[25] There are multiple potential forms of clinical utility, including but not limited to early commencement of directed or supportive therapy, reproductive and family planning, living-related kidney transplantation, avoidance of invasive investigations and futile therapies, and conclusion of an otherwise prolonged diagnostic odyssey.[26] While for any individual patient or family, the type, form, timing, and magnitude of clinical utility can vary, there is a growing consensus of broad overarching benefit within a person-centered model of care, though some barriers to generalizable implementation persist.[25,27] While clinical research has linked GKD to earlier detection and persistent contribution to kidney failure incidence and prevalence,[18] there is no evidence on the comparative healthcare utilization outcomes between GKD and other types of CKD. Such information would offer a useful perspective on healthcare needs trajectories, enabling better healthcare system planning, investment, and resource allocation.

The aim of this study was to determine if clinically ascribed GKD is associated with distinct patterns of inpatient care utilization compared to non-genetic CKD. As such, we undertook a retrospective cohort study with the characteristic of interest being GKD and the outcome of interest being hospitalizations (likelihood and intensity as expressed in Australian dollars). Based on prior knowledge of CKD epidemiology, in particular heterogeneous and often faster progression in GKD,[28,29] we hypothesized that GKD would be associated with a greater need for hospital care as reflected in admission records. If systematic differences were confirmed, the secondary aim was to measure the effect of GKD, relative to other types of CKD, on inpatient admissions and their resource intensity. This was to be done considering variation in all-cause admissions as well as selected sub-groups of admissions, with the overarching goal of advancing our understanding of specific needs and causes underlying the distinct patterns of hospital care utilization in GKD.

Materials and Methods

Cohort

The analyzed sample represented the CKD population in Queensland, Australia, combining individuals enrolled in the Chronic Kidney Disease Queensland (CKD.QLD) Registry[30] and a matching sample of those who had been admitted to a public or private hospital in Queensland with a record of CKD diagnosis. Australia has a universal healthcare system, making the sample representative of the population at large. For the sample population (n = 29,046), we analyzed a complete record of 809,188 public and private hospital inpatient episodes that took place between 1 July 2011 and 30 June 2018. The design of the linked dataset, details of the data collection, and ethical approval details have been previously described.[31]

Case selection

CKD of potential monogenic origin was identified from the patient's records using International Classification of Diseases (ICD) diagnosis codes for forms of GKD (D57/E85/N02/N07/N25/P96/Q60-64/Q85/Q87/Z84). This includes potentially heritable disorders that may include a kidney component or phenotype, either primary or secondary.[17,18,29,32] It also includes instances where an affected individual might present in childhood but subsequently reach adulthood. Importantly, these are clinically derived diagnoses, and information as to whether these are informed or not by diagnostic genomic testing was not recorded. We identified key CKD comorbidities using ICD-10-Australian Modification Australian Classification of Health Interventions.[33]

Clinical outcomes

All-cause inpatient admissions were the primary outcome of interest. In addition, we sought to explore specific types of episodes reflecting different healthcare needs and categories of health conditions. Specifically, we made a distinction between medical and surgical admissions, based on an admissions classification system compiled by the Australian Independent Hospital Pricing Authority.[34] Furthermore, we explored 10 thematic sub-groups of causes for admissions that included kidney (kidney failure, CKD other than kidney failure), infections, cardiovascular conditions, trauma and emergency, immunological conditions, psychiatric and neurological disorders, respiratory problems, cancers, and, gastrointestinal and liver issues. Definitions of these groups are available in Supplemental Table 1. A descriptive summary of the dataset was performed, including statistical tests for differences between the GKD and non-GKD groups (χ^2 [Chi-squared] and t-tests), regarding known sociodemographic characteristics, health variables, and utilization outcomes.

Clinical characteristics

The dataset included administrative records including patient demographics, place of residence, diagnoses, admission dates, relevant outlays incurred by the public payer, and deaths. The information was sourced from the Queensland Hospital Admitted Patient Data Collection, which details the causes and course of inpatient admissions, activity-based funding data, in which payments corresponding to costs of hospital episodes are determined using the Australian-Refined Diagnosis-Related Groups-6.x hospital system, and Queensland Registrar General Deaths. All coding within this Data Collection is entered by professional qualified clinical coders at all hospitals and health services in Queensland at the end of each episode of care based upon the clinical entries of the treating clinicians for that episode of care.

Analytic approach

Testing the research hypotheses and estimating effect sizes required an analytical approach to eliminate confounding sources of outcome variation, and employing methods appropriate for longitudinal data. We converted daily admission records into a quarterly panel dataset, an established method for analyzing healthcare utilization patterns.[35] For each person captured in the study, we aggregated all admissions on record over 3-month periods starting 1 July 2011. For each quarter, we generated 2 utilization outcome variables: (1) a binary variable representing an occurrence of at least 1 admission, and (2) the cost of hospital admissions approximated by Australian-Refined Diagnosis-Related Groups-based payments. The relationship between the 2 outcomes can be represented as:

$$y = \begin{cases} 0 \; if \; h = 0 \\ y^* \; if \; h = 1 \end{cases} \quad (1)$$

where h denotes the occurrence of 1 or more hospitalization events and is a binary random variable that can be modeled using a logistic regression. For quarters in which $h = 1$, the resulting cost y^* can be modeled using a generalized linear model.

To analyze variation in such defined outcomes, we employed a 2-part multivariate regression model selected from alternative approaches (for example, a hurdle model) on the basis that nil observations were genuine zeros (rather than missing or non-response) and that participation did not influence the intensity of utilization.[36] Specifically, the 2 parts involved (1) a logistic regression for binary outcomes in a panel dataset to analyze variation in the quarterly likelihood of admission (h in Eq.1); and (2) a log-linear panel regression to analyze variation in the quarterly cost of admitted care (y^* in Eq.1). The model can be summarized as:

Part 1 (likelihood of admission):

$$\Pr(y > 0|\mathrm{x}) = \phi(\mathrm{x}'\delta)$$

Part 2 (cost of admission):

$$E[\ln(y)|y > 0, \mathrm{x}] = \mathrm{x}'\beta \quad (2)$$

where ϕ is specified as logit, x is a vector of explanatory variables and δ and β represent respective vectors of coefficients to be estimated. Log transformation was used to normalize the distribution of observed cost values, which implies that zero cost values were removed from the analysis. Consequently, the interpretation of results for the cost outcome was conditional on having at least 1 admission, which is a standard feature of a 2-part model. Costs were indexed forward to 2017-18 using the health sector inflation rate to eliminate price increases as a source of cost variation.[37] Robust standard errors were calculated to safeguard against heteroskedasticity and residuals were inspected post-estimation for normality of distribution.

Explanatory analyses

In determining which explanatory variables (x in Eq.2) were to be included in the model, we considered the behavioral model of access to medical care that suggests that genetic factors would be only 1 of many determinants of inpatient utilization.[38] Thus, to enable drawing inferences regarding the role of GKD in driving inpatient admissions, the statistical model had to control for confounding factors related to a person's environment, sociodemographic characteristics, needs, and health behaviors. Accordingly, our set of explanatory variables represented a range of relevant factors

concerning the patient's demographics (age, sex, and indigenous status), health status (CKD stage, comorbidities), social environment (socioeconomic group), access to health care (area of residence, enrolment in a public renal specialty clinic), system-wide trends over time (year of admission) and, for those who died, the change in use of hospital care associated with death (quarters to death). The variables of interest relevant to the testing of our research hypotheses were GKD status (binary), study quarter (range 1-28), and their interaction.

Because study consent was retroactive in giving access to individuals' admissions history, all participants were analyzed over the entire study period, regardless of the time of their consent. Quarterly outcomes were removed from the panel after a person's death. The panel dataset was thus unbalanced with observations not missing at random. However, this did not introduce bias because death was the only cause of missing observations, and zero outcomes recorded in those who died were no longer relevant to the analysis.

Random- and Fixed-effects models

We used the Breusch-Pagan Lagrange multiplier test to rule out the possibility of ordinary least-squares regression, and the Hausman test to determine preference between the random- and fixed-effects specifications. It is important to note that the fixed-effects approach enables estimating the GKD-study quarter interaction term but not the coefficient of GKD alone due to the latter being time-invariant. Critically, understanding the full effect (ie, estimating the intercept and the trend term) of GKD on the likelihood and cost of admissions would only be possible using a random-effects model. Consequently, the statistical analysis strategy assumed that results from both fixed- and random-effects models would be estimated, and the preferred model indicated based on the Hausman test, noting any significant differences in their results. Regarding the possibility of the data having a latent multilevel structure, we note that bias-adjusted multilevel models and fixed effects produce identical results for the shared coefficients and therefore lead to consistent conclusions.[39]

Two sets of regression results are thus presented, each approach comprising a 2-part model explaining variation in the likelihood and cost of inpatient admissions (Table 1). For the likelihood outcome, coefficients are presented as odds ratios. For the cost outcome, model coefficients obtained for log-transformed results are exponentiated to enable interpretation as the percentage increases over reference values. Figure 1 presents predicted probabilities and log-transformed costs of admissions over time, computed at mean values for all explanatory variables in the study sample except proximity to death, which was held at zero. The graphs labeled 'all admissions' are a visualization of marginal effects corresponding to the primary outcome analysis presented in Table 1. The remaining graphs represent analyses performed on subsets of admissions indicated by their respective labels. *P* values shown in this figure indicate if GKD is statistically significantly different from non-GKD over the study period.

Results

At the beginning of the study period, patients with GKD were considerably younger (mean age 58.2 vs 70.9 years in non-genetic), had higher socioeconomic status (40.7% in top 2 quintiles, vs 36.2%), had more advanced disease (27.8% at CKD stage 4 or 5, vs 10.3%), and were less likely to have diabetes (9.8% vs 25.4%) or cardiovascular disease (10% vs 18.7%) (Table 2) than other CKD patients. They were more likely to be under public renal specialist management, as indicated by enrolment in the CKD.QLD registry (45.8% vs 24.8% in non-genetic) and were less likely to die during the 7-year study period (21.9% vs 37.5%). We did not find statistically significant differences between the 2 groups in terms of gender (56.1% male, vs 54% in non-genetic), indigenous descent (3.2% vs 4.8%), remoteness of residence (51.8% in metropolitan areas, vs 49.4%) or hypertension (26.8% vs 24.4%). Over the study period, the GKD group had a consistent record of more admissions (the mean excess annual number of admissions over the comparator group increasing from 5.2 in year 1 to 13.4 in year 7) and more costly admissions (mean excess annual cost over comparator increasing from $5265 in year1 to $12,993 in year7).

In the random-effects specification, adjusting for other factors (Table 1), individuals with GKD had 1.36 (95% CI: 1.20-1.54) higher odds of admission in any quarter, with odds further increasing by 1.013 (1.008-1.018) per quarter above the statistically significant trend for non-GKD of 1.035 (1.034-1.036) per quarter (model i). With respect to costs, the quarterly trend for GKD was 2.3% (1.3%-3.4%) above the non-GKD trend of costs increasing by 1% percentage point (0.9%-1.2%) per quarter. The GKD constant was not statistically significantly different from zero in this model, ie, there was no difference in the intercept term (model ii).

In the fixed-effects model, the odds of admission for GKD increased by 1.01 (1.01-1.02) per quarter above the non-GKD trend of increasing 1.02 (1.01-1.04) per quarter (model iii). For the cost outcome, the trend coefficient for GKD was an additional 1.8% (0.6%-3.0%) per quarter. The slope of the corresponding trend for non-GKD was not statistically significantly different from zero (model iv). Based on the results of statistical tests, we rejected the null hypotheses that the difference between fixed and random-effects estimates was not systematic for both the likelihood model (χ^2 (18) = 1422.33; P = .0000) and the cost model (χ^2 (18) = 879.58; P = .0000), giving preference to fixed-effects. Residuals from random- and fixed-effects models displayed a high degree of normality, indicating

Table 1 Factors explaining the likelihood and cost of inpatient admissions – results from multiple regression analyses of quarterly panel data

	RANDOM EFFECTS								FIXED EFFECTS							
	Probability Model (i)				Cost Model (ii)				Probability Model (iii)				Cost Model (iv)			
	OR	*P*	95% CI		Coef.	*P*	95% CI		OR	*P*	95% CI		Coef.	*P*	95% CI	
GKD	1.3566	**.0000**	1.1987	1.5353	0.0701	.4730	-0.1213	0.2615	NE				NE			
Study quarter	1.0347	**.0000**	1.0338	1.0356	0.0103	**.0000**	0.0087	0.0120	1.0241	**.0110**	1.0055	1.0431	-0.0051	.6830	-0.0297	0.0195
GKD*quarter	1.0129	**.0000**	1.0076	1.0182	0.0232	**.0000**	0.0125	0.0339	1.0125	**.0000**	1.0071	1.0180	0.0177	**.0040**	0.0057	0.0298
Age	1.0006	.2400	0.9996	1.0017	-0.0099	**.0000**	-0.0111	-0.0087	1.0662	.0870	0.9908	1.1474	0.0979	**.0500**	0.0000	0.1957
Male	1.0829	**.0000**	1.0530	1.1137	0.0585	**.0000**	0.0270	0.0899	NE				NE			
Indigenous	1.3924	**.0000**	1.3081	1.4823	0.2298	**.0000**	0.1600	0.2996	NE				NE			
Registry	1.1517	**.0000**	1.0964	1.2098	-0.0753	**.0050**	-0.1276	-0.0230	NE				NE			
CKD stage																
1	ref.				ref.				NE				NE			
2	1.0606	.4670	0.9051	1.2429	0.2586	**.0020**	0.0966	0.4205	NE				NE			
3	1.2262	**.0030**	1.0696	1.4057	0.3660	**.0000**	0.2279	0.5042	NE				NE			
4	1.6518	**.0000**	1.4338	1.9030	0.5571	**.0000**	0.4144	0.6999	NE				NE			
5	3.3268	**.0000**	2.8610	3.8685	1.0561	**.0000**	0.9000	1.2123	NE				NE			
(missing)	2.1555	**.0000**	1.8764	2.4761	0.5076	**.0000**	0.3656	0.6497	NE				NE			
Diabetes	1.1318	**.0000**	1.1075	1.1565	0.2289	**.0000**	0.1989	0.2589	1.1188	**.0000**	1.0885	1.1499	0.3708	**.0000**	0.3186	0.4230
Cardiovascular	1.1774	**.0000**	1.1530	1.2024	0.6558	**.0000**	0.6264	0.6853	1.2032	**.0000**	1.1766	1.2305	0.7237	**.0000**	0.6875	0.7598
Hypertension	0.9434	**.0000**	0.9256	0.9616	0.5489	**.0000**	0.5208	0.5770	0.9520	**.0000**	0.9329	0.9715	0.5447	**.0000**	0.5114	0.5781
Quarters to death																
1	3.7975	**.0000**	3.6333	3.9691	0.6706	**.0000**	0.6162	0.7249	2.8928	**.0000**	2.7658	3.0256	0.4530	**.0000**	0.3813	0.5247
2	1.9664	**.0000**	1.8841	2.0522	0.7348	**.0000**	0.6648	0.8048	1.5734	**.0000**	1.5066	1.6430	0.4490	**.0000**	0.3632	0.5348
Socioeconomic quintile																
bottom	ref.				ref.				NE				NE			
2nd	1.0536	**.0030**	1.0175	1.0910	0.0685	**.0020**	0.0254	0.1116	NE				NE			
middle	1.0423	**.0450**	1.0010	1.0853	0.0070	.7900	-0.0444	0.0584	NE				NE			
4th	1.0098	.6160	0.9720	1.0491	0.0260	.3130	-0.0245	0.0766	NE				NE			
top	1.0749	**.0000**	1.0369	1.1144	0.0864	**.0000**	0.0386	0.1342	NE				NE			
(missing)	0.8296	**.0000**	0.7725	0.8910	0.1330	**.0030**	0.0455	0.2205	NE				NE			
Area remoteness																
metro	ref.				ref.				NE				NE			
regional	0.9424	**.0010**	0.9107	0.9753	0.0396	.0780	-0.0045	0.0837	NE				NE			
rural	0.8904	**.0000**	0.8587	0.9233	0.1960	**.0000**	0.1553	0.2366	NE				NE			
remove/very remote	0.8226	**.0000**	0.7635	0.8863	0.2648	**.0000**	0.1862	0.3433	NE				NE			
(missing)	0.8042	**.0000**	0.7675	0.8426	-0.0532	.1400	-0.1240	0.0175	NE				NE			
Constant	0.0864	**.0000**	0.0743	0.1003	8.5739	**.0000**	8.4167	8.7312	NE				1.6729	0.6240	-5.0243	8.3701
N groups	27,678				23,886				26,410				23,886			
N obs	643,223				69,567				630,711				69,567			
Test stat	Wald Chi^2 (26) = 15239.25				Wald Chi^2 (26) = 7936.99				LR Chi^2 (8) = 14719.99				F (8,23885) = 648.73			
P value	.0000				.0000				.0000				.0000			

The boldface values are the *P* values that reached statistical significance.

CKD, chronic kidney disease; *Coef*, coefficient; *GKD*, genetic kidney disease; *NE*, not estimable; *OR*, odds ratio.

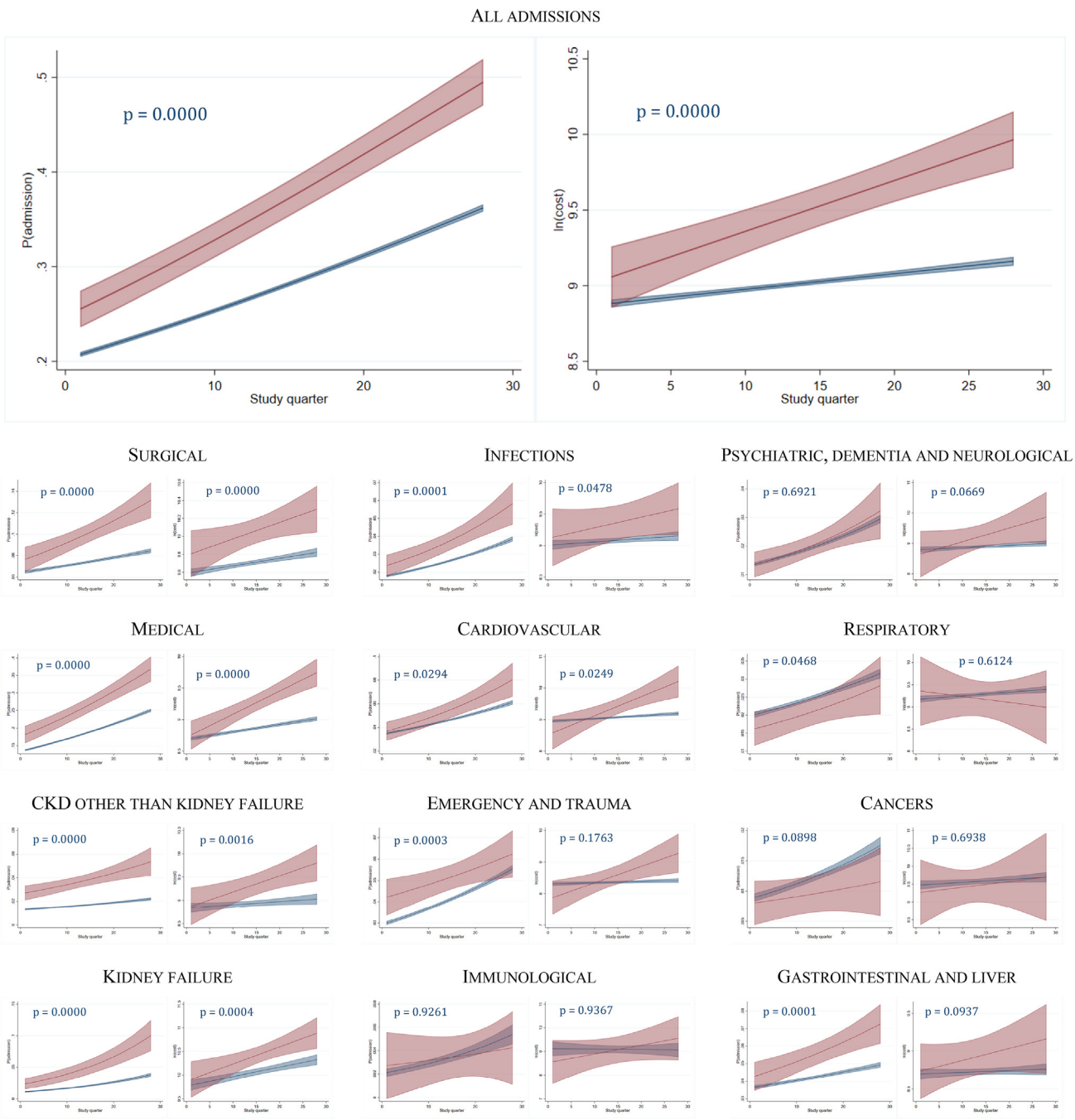

Figure 1 Adjusted predictions (95% CIs) of likelihood (left) and cost (right) of admissions over the study period, for GKD (in red) and non-GKD (in blue), by the scope of admissions. *GKD*, genetic kidney disease

that the log transformation of the outcome variable had been successful in preventing the violation of model assumptions (Supplemental Figure 1).

In considering specific groups of causes for admissions, we found statistical evidence of GKD having a higher than non-GKD likelihood and cost for both surgical and medical admissions, kidney failure, CKD other than kidney failure, infections, and cardiovascular conditions (Figure 1). This was reflected in the differences in the order and proportion of the top 10 admission diagnosis-related groups (DRGs) amongst non-GKD and GKD groups (Supplemental Table 2). Despite a significantly lower total annual length of hospital stay per person for those without GKD than for those with GKD, this difference mostly equalized upon censoring for admissions due to dialysis (Supplemental Table 3, Supplemental Table 4). Additionally, we found evidence of GKD having a higher likelihood, but not cost, of admissions due to emergency and trauma, respiratory, gastrointestinal, and liver conditions. We did not find evidence of between-group differences in admission patterns

Table 2 Baseline characteristics of study population

	Non-GKD	GKD	*P* value
n (%)	28,474 (98.0)	572 (2.0)	
SOCIO-DEMOGRAPHIC CHARACTERISTICS			
Male, *n* (%)	14,660 (54.0)	307 (56.1)	.3310
Age, mean years (SD)	70.9 (14.4)	58.2 (17.9)	**.0000**
Age bands, *n* (%)			**.0000**
<40	1,122 (0.3)	90 (205.1)	
40-49	1,298 (0.3)	76 (237.3)	
50-59	2,778 (0.4)	102 (507.9)	
60-69	5,577 (0.4)	117 (1019.6)	
70-79	8,222 (0.4)	105 (1503.1)	
≥80	8,134 (0.2)	57 (1487.0)	
Indigenous, *n* (%)	1,218 (4.8)	15 (3.2)	.0950
Socioeconomic group			**.0170**
Bottom quintile	9,086 (31.9)	160 (28.0)	
2nd quintile	4,556 (16.0)	85 (14.9)	
Middle quintile	2,964 (10.4)	73 (12.8)	
4th quintile	4,094 (14.4)	86 (15.0)	
Top quintile	6,201 (21.8)	147 (25.7)	
(missing)	1,573 (5.5)	21 (3.7)	
Area remoteness			.1570
Metropolitan	14,077 (49.4)	296 (51.8)	
Regional	5,470 (19.2)	117 (20.5)	
Rural	5,616 (19.7)	108 (18.9)	
Remote/very remote	902 (3.2)	9 (1.6)	
(missing)	2,409 (8.5)	42 (7.3)	
HEALTH VARIABLES			
CKD stage, n (%)			**.0000**
1	310 (1.1)	15 (2.6)	
2	644 (2.3)	17 (3.0)	
3	3,893 (13.7)	104 (18.2)	
4	2,012 (7.1)	80 (14.0)	
5	924 (3.3)	79 (13.8)	
(missing)	20,691 (72.7)	277 (48.4)	
Kidney transplant	224 (0.8)	46 (8.0)	
Diabetes, n (%)	7,231 (25.4)	56 (9.8)	**.0000**
Cardiovascular, n (%)	5,333 (18.7)	57 (10.0)	**.0000**
Hypertension, n (%)	6,939 (24.4)	153 (26.8)	.1900
CKD.Qld Registry cohort, n (%)	7,059 (24.8)	262 (45.8)	**.0000**
Death, n (%)	10,689 (37.5)	125 (21.9)	**.0000**
HOSPITAL ADMISSIONS			
Annual number of admissions per person, mean (SD)			
2011-12	3.0 (14.9)	8.2 (28.8)	**.0000**
2012-13	3.4 (15.8)	9.2 (29.2)	**.0000**
2013-14	3.8 (17.0)	11.8 (34.8)	**.0000**
2014-15	4.4 (18.6)	14.0 (37.6)	**.0000**
2015-16	5.0 (20.2)	17.8 (42.4)	**.0000**
2016-17	5.9 (22.1)	18.0 (41.3)	**.0000**
2017-18	6.6 (23.7)	20.0 (44.6)	**.0000**
Annual hospital costs per person, mean A$ (SD)			
2011-12	8,992 (32,753)	14,257 (43,295)	**.0040**
2012-13	9,946 (33,436)	15,301 (37,351)	**.0008**
2013-14	10,409 (33,506)	17,351 (42,034)	**.0001**
2014-15	12,084 (36,930)	19,795 (52,673)	**.0008**
2015-16	13,357 (38,875)	23,429 (50,190)	**.0000**
2016-17	15,096 (41,336)	28,539 (58,669)	**.0000**
2017-18	14,979 (37,249)	27,971 (53,340)	**.0000**

Study years align with financial years in Australia that run from 1 July to 30 June the following year. The boldface values are the *P* values that reached statistical significance.

A$, Australian dollar, *CKD*, chronic kidney disease; *GKD*, genetic kidney disease.

due to any of the remaining causes (ie, immunological; psychiatric, dementia neurological; and cancers) we controlled for.

Discussion

The increasing availability of genetic testing means that a quicker and more precise distinction can now be made between CKD of monogenic and other origins.[40] Because obtaining this information remains costly, healthcare payers, including governments and insurers, are faced with the question of whether this information should be funded on the grounds of clinical and personal utility, and cost-effectiveness. Our study is the first comprehensive, large-sample attempt to explore the patterns of hospital admissions in GKD as compared to non-genetic CKD. The results demonstrate that individuals with GKD have a higher likelihood and cost of hospital admissions and that the gap between the 2 groups increases over time. The findings of this study reinforce the value of identifying GKD as a primary cause of CKD.

While the impact of GKD on the age of onset and CKD progression varies depending on specific disorder, gene, and variant,[28] when considering inpatient utilization metrics, we find evidence of effects for the broad class of GKDs that is consistent across multiple specific causes. There is very early and persistent divergence in both the likelihood of hospital admission and the cost of admissions between those with GKD compared to other forms of CKD (Figure 1). This observation remains even when examining individuals who experienced kidney failure versus earlier stages of CKD. Given the substantial health costs involved in kidney replacement therapy,[41,42] this extends insights into substantial health service utilization burden in earlier stages. Furthermore, it highlights that regardless of the stage of CKD experienced, a patient affected by GKD is more likely to experience hospital admission and greater admission costs than other patients.

These insights are difficult to apply without understanding of potential or granular drivers of these differences. At a high level, this divergence in likelihood and cost of admission is reflected concurrently by similar and symmetrical divergence between both surgical and medical reasons for admission (Figure 1) and inpatient costs over time (Supplemental Figure 2). At a finer level, compared to other causes, admissions attributable to cardiovascular disease and infections appear to contribute significantly to an excess of hospital admission likelihood and cost for those with GKD. This is in spite of the fact that people affected by GKD have a lower prevalence of both cardiovascular disease and diabetes, with potential alternate contributors including a longer time exposure to CKD owing to younger age at onset. The underpinning factors for this may additionally include cardiovascular disease in the setting of longer time-burdens of CKD due to GKD or multisystem forms of GKD, and infections may relate to immunosuppressive medications related to kidney transplantation or presumptive immunosuppressant treatments for some glomerular disorders that may alternatively have non-monogenic aetiologies. While an initial inspection on a prevalence basis may suggest only a modest indication for cardiovascular risk factor management amongst those with GKD, hospital admission, and cost characteristics instead indicate that this might be significantly prioritized in this group. These findings are generally in keeping with previous reports indicating substantial cardiovascular disease risk and sequelae amongst younger patients with kidney failure,[43] including increased hospitalization.[44] Our findings extend this to be a comorbidity, whether prevalent or incident, of particular interest for hospital admission and cost in those with GKD.

In respect of other potential drivers of admissions and costs, cancer, immunological disease, psychiatric conditions, dementia, and neurological disorders do not appear to be explanators of the higher admission probabilities and costs experienced by patients with GKD. This is not to say that these conditions do not contribute overall to the hospitalization needs of people with CKD, but rather that this is not experienced differently by those affected by GKD. Alternatively, respiratory, emergency trauma, and gastrointestinal and liver disorder-ascribed reasons for admission did result in excess likelihood of admission for those with GKD but without significant increases in cost. These findings remain relevant and further understanding of these phenomena over time may present new opportunities to modify the burden of hospitalizations, to the extent these factors represent avoidable admissions.

The prognostic and predictive usefulness of this information has so far been limited for both genetic and non-genetic CKD. This was highlighted by the Medical Services Advisory Committee (MSAC), an Australian health technology assessment body, which supported in 2021 the public funding of genetic testing for heritable kidney diseases. The cohort we describe in this study has had clinically ascribed diagnoses and whether these diagnoses were genomically informed or not was not recorded. Further, the cohort and its health service utilization characteristics were entirely from before the implementation of this MSAC recommendation for Australian public funding of diagnostic genomic testing for suspected heritable kidney disease in July 2022. It is a limitation that any genetic testing costs are not identifiable in this cohort, but are likely to have been low in the absence of their public subsidization at that time, and any such genetic testing costs for suspected GKD would have been experienced predominantly by the clinically coded GKD group. This would have further increased the potential differences in health service and resource utilization between the non-GKD and GKD groups. While the benefit of improved reproductive planning provided sufficient grounds to justify public funding, MSAC's advice also recognized limited benefits relating to prognostic and predictive validity and clinical utility of

genetic testing.[45] Similarly, in 2018, MSAC supported public funding of genetic testing in Alport syndrome, justifying it with several potential benefits, however, no utility for improved clinical management or healthcare planning was identified as relevant to the decision.[46]

We anticipate that understanding differential health and healthcare trajectories will have several important implications. It may aid proactive identification of individuals who are predictably higher future users of hospital care while warranting dedication resources for secondary prevention to slow progression and reduce downstream healthcare system consequences. It may identify priority areas for future research to improve patient outcomes, inform health system organizations, and influence public willingness to resource technologies and services that enable early diagnosis, primary and secondary prevention, or offer effective mitigation measures. Our results are relevant for health technology assessment of diagnostics and treatments, including economic evaluation of interventions that rely on models of disease progression and seek to identify treatments with the highest return on investment.

Interpreting differences between random- and fixed-effects models involves performing a statistical test, understanding the problem being modeled, and comparing the results of the competing models. The statistical tests indicate that the fixed-effects model is to be preferred, in particular, because this model is less likely to suffer due to omitted variables. As such, we consider its results the most robust evidence of effects attributable to GKD. However, a drawback of the fixed-effects model is that it does not allow for the estimation of time-invariant factors, which is problematic considering the purpose of this study. The random-effects model addresses this issue by enabling estimation of the GKD coefficient as well as other medical and non-medical factors affecting the need for, and the ability to reach inpatient care. Our random-effects model affords a comprehensive specification that controls for other sources of outcome variation, with a strong theoretical basis provided by the behavioral model of access to health care. A further justification for the use of random effects lies in the fact that the outcome variations between individuals and across time can be plausibly interpreted to be caused by individual-specific errors rather than intercepts, which also enables the drawing of inferences about the broader population. Comparing the results of the 2 models, we conclude the findings are consistent between the 2 specifications, and differences in coefficient estimates are small, suggesting that the potential omitted variables problem may be minor. This consistency of findings between the more robust fixed-effects and the more flexible random-effects approach gives high confidence in the overall findings.

A notable strength of this study is its large, comprehensive, and complete dataset that tracked more than 29,000 individuals over 7 years while allowing to control for a range of confounding factors. The length of the dataset is particularly important in studying rare traits, with GKD found in only 2% of our sample population. Its width enables drawing conclusions about long-term healthcare trajectories. Potential limitations relate to the exclusion of other healthcare settings, notably primary and outpatient care. While the sample draws from a CKD population at large, it is likely to be biased toward more advanced CKD that warrants specialist management or is diagnosed during hospital episodes and may underemphasize earlier stages of CKD. With respect to GKD, the sample is representative of a population identified from the information existing in hospital records including a contemporary broad definition of GKD aligned to all potential monogenic disorders that might include a kidney component or phenotype, either primary or secondary. A potential limitation is the relative admixture of different disorders including those that are kidney-limited in addition to those that are multisystem, and those of a minority as well as majority monogenic basis. The availability of this information in admitted patient information systems may both underreport and underrepresent the GKD population at large, which would explain why the prevalence of GKD in our sample is lower than that found in prevalence studies.[17,18] This extends to the possibility of some cases missing a record of diagnosis, or their diagnosis being mis-coded. This issue is mitigated by 2 considerations. Firstly, we compared GKD to other CKD, rather than to the general admitted population, which means there may be consistency between the groups in terms of the availability of identifying information, and secondly, there are no clear reasons why such underrepresentation would bias results in either direction. Regardless, there is a clear need to urge and support the accuracy of clinical diagnostic coding in health services given that this is real-world data used by health system administrators, policy-makers, and funders in order to lead health system operations and planning. Further targeted chart audit or review within an individual health service or centre may assist in replicating these findings, in addition to replication in other health systems or services domestically and internationally. Nevertheless, the data presented is real-world and reflective of clinical practices at scale across a large universal healthcare system spanning 16 hospitals and health services and thousands of clinicians. Importantly, the evidence we present may provide additional reasons for genetic testing in CKD to become more commonplace, enabling future study samples to more accurately represent the underlying issue. Our findings provide additional background for future pre-/post-cost-effectiveness research and studies that are required to evaluate genomic testing for clinically suspected GKD.

The precise estimates are, nevertheless, unlikely to be easily generalizable outside Australia in a specific sense, for several reasons. A large portion of the system burden of CKD takes the form of kidney replacement therapies, which in Australia is predominantly a same-day, inpatient procedure. Moreover, the use of home-based dialysis is relatively common in Australia. In other countries, notably in the US, dialysis is primarily provided in the outpatient setting, and reliance on home-based dialysis is limited, resulting in distinct admission patterns. Secondly, Australians enjoy a well-resourced healthcare system and high levels of

accessibility to inpatient care owing to a comprehensive public universal healthcare system alongside a high uptake of private health insurance. Utilization patterns are likely to be systematically different in countries where hospitals operate under considerable resource constraints or where health insurance coverage is restricted. Thirdly, as Australia operates a customized diagnosis-related group system for determining hospital payments, the cost estimates reported in this study may be dissimilar elsewhere, due to differences in the costs of labor and capital, for example. Still, our results are likely to be generalizable in a broader sense, to the extent that recorded admissions reflect the relative occurrence (likelihood) and intensity (cost) of healthcare needs in the 2 respective groups.

This is an initial analysis at a high level which opens further lines of questioning for subsequent in-depth analyses as well as replication elsewhere. Specific areas could include analysis of relative differences between specific GKDs and whether some, such as polycystic kidney disease, are the major contributors, including interactions of specific GKD, overlapping or exclusive ICD-10 codes, majority or minority monogenic GKD ICD-10 codes, age, CKD stage, admission type, treatment type, and outcomes. In the interim, polycystic kidney disease accounted for roughly half of our GKD group, as expected, with the same and significant overall patterns and costs of admissions in line with the overall GKD group. Further exploration is indicated around the potential interaction of increased prevalence of kidney transplantation (Table 2) amongst those with GKD given the potential for increased hospitalization in the initial short-medium term post-transplantation, and around length of stay and cost censored for dialysis (Supplemental Table 3, Supplemental Table 4). Furthermore, as this analysis is of data derived from the activity-based funding environment of the Australian healthcare system, a similar analysis of the Medicare Benefits Scheme environment would be complimentary especially now that specific genomic testing item codes have been implemented for reimbursement.

In conclusion, GKD is a readily identifiable factor associated with increased long-term healthcare needs and demand for hospital care. This encourages healthcare redesign and calls for additional resources to be dedicated to the diagnosis, prevention, and treatment of GKD. There is also clearly a need for accurate clinical diagnostic coding in health systems. Understanding long-term healthcare trajectories creates opportunities for better planning, allocation, and investment decisions, with the goal of alleviating downstream healthcare system pressures and offering a prospect of better health outcomes for affected patients and families.

Data Availability

The primary data underpinning this analysis is not able to be shared publicly due to the Public Health Act (QLD) approval governing its release to the investigators. The authors (P.M.S. and A.J.M.) can be contacted in regard to this if required as targeted Public Health Act (QLD) amendment applications can be placed to seek access to a deidentified dataset for targeted and prospectively approved purposes.

Acknowledgments

The authors would like to acknowledge researchers in the NHMRC CKD Centre of Research Excellence, site coordinators and staff contributing to the CKD.QLD Registry, and the Queensland Health Statistical Services Branch, who contributed to the collection of the linked dataset analysed in this study.

Funding

The study was supported by the National Health and Medical Research Council (NHMRC) grant #1079502. A.J.M. was supported by a Metro North Hospital and Health Service Clinical Research Fellowship and a Queensland Health Advancing Clinical Research Fellowship.

Author Contributions

Conceptualization: P.M.S., A.J.M.; Data Curation: P.M.S., A.J.M.; Formal Analysis: P.M.S., A.J.M.; Funding Acquisition: L.B.C.; Investigation: P.M.S., A.J.M.; Methodology: P.M.S., A.J.M., L.B.C.; Project Administration: P.M.S., A.J.M.; Resources: A.J.M., L.B.C.; Software: P.M.S., L.B.C.; Supervision: L.B.C.; Validation: P.M.S., A.J.M., L.B.C.; Visualization: P.M.S., A.J.M.; Writing-Original Draft: P.M.S., A.J.M.; Writing-Review & Editing: P.M.S., A.J.M., L.B.C.

Ethics Declaration

This study is a sub-study of the CKD.QLD Registry (HREC/15/QRBW/294), which has been approved by Metro North Human Research Ethics Committee and University of Queensland Medical Research Ethics (Number: 2011000029). All CKD.QLD Registry participants provided informed consent for the collection, storage and analysis of their health data. The study of the QH held datasets of CKD patients, both those in the CKD.QLD Registry and the comparison patient cohort, listed in this study is through an ethically approved waiver of consent according to the National Health and Medical Research Council (NHMRC) National Statement on Ethical Conduct in Human Research. In addition, a Public Health Act application (RD006802)

was approved to access all hospitalization information of the CKD.QLD Registry patients.

Conflict of Interest

The authors declare no conflicts of interest.

Additional Information

The online version of this article (https://doi.org/10.1016/j.gimo.2024.101876) contains supplemental material, which is available to authorized users.

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