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Hip fractures in elderly patients with non-dialysis dependent chronic kidney disease

Outcomes in a Southeast Asian population

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Abstract

Chronic kidney disease (CKD) causes bone and mineral disorders and alterations in vitamin D metabolism that contribute to greater skeletal fragility. Hip fracture in elderly is associated with significant morbidity and mortality. The aim of this study was to investigate the outcome of elderly patients with non-dialysis dependent CKD and hip fracture undergoing surgery.

Retrospective study with IRB approval of patients above 65 years of age, with hip fractures admitted between June 2014 to June 2016 in a Southeast Asian cohort. Data collected included demographic variables and the haematological and biochemical parameters HBA1c, estimated glomerular filtration rate (eGFR), serum calcium, phosphorous, and 25(OH) Vitamin D. Co-morbidities investigated were ischemic heart disease, congestive heart failure, peripheral vascular disease, malignancy, chronic obstructive pulmonary disease, cerebro vascular accident, hypertension and hyperlipidaemia. All patients were followed up from index date to either death or June 1, 2018.

Of the 883 patients, 725 underwent surgery and 334 had CKD. Death rates for CKD patients with hip fractures and those with normal renal function did not differ significantly [8.08% vs 6.54%, (HR=1.33, 95% CI: 0.95, 1.86; $P=.102$)], whilst median hospital length of stay was significantly higher in CKD patients [10.5 vs 9.03 days ($P=.003$)]. Significant risk factors associated with higher risk of mortality in the elderly with hip fracture were male gender, age ≥80 years and serum albumin <30 g/L (all, $P<.0001$).

In summary, in elderly, non-dialysis dependent CKD patient with hip fracture we found that male gender, age ≥80 years, low serum albumin and eGFR <30 mL/min/1.73 m^2 were associated with higher risk of death. The hospital stay in the CKD group was also longer. Additional studies are needed to validate our findings.

Abbreviations: CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate.

Keywords: chronic kidney disease, elderly hip fracture, survival

1. Introduction

An aging population worldwide poses major challenges to healthcare systems. Elderly patients are at increased risk of falls and hip fractures due to increasing age, medications, cognitive impairment, and comorbidities. Hip fractures in the elderly are associated with significant mortality and physical dependency. In the elderly presence of CKD itself is one of the multiple risk factors leading to poor outcome.

Available literature reports 1-year mortality of 15% to 40% in elderly patients with hip fracture and no kidney disease.[1,2]

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We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Sing Health Centralized IRB approved our study for data collection and waiver of consent was obtained due to retrospective nature of the study.

The work has been carried out in accordance with Code of Ethics of the World Medical Association.

The manuscript is in line with Recommendations for the Conduct, Reporting, Editing and Publications of Scholarly Work in Medical Journals.

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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Chronic kidney disease (CKD) is of particular concern in the elderly population.[3,4] Chronic kidney disease with its effects on Vitamin D metabolism as well as divalent ion metabolism is known to contribute to skeletal fragility.[5,6] The risk of hip fracture increases with worsening kidney function and is highest in CKD 5 and dialysis patients. While dialysis dependent patients with hip fracture have a mortality of 50% to 64%,[7–9] the effects of non-dialysis dependent CKD (G3–5) on the outcome in this group of patients has also been studied,[10–12] however most of the earlier studies have been predominantly in a Caucasian population. In this study we report on the effects of worsening CKD on mortality in elderly patients with hip fracture in a Southeast Asian population.

1.1. Study AIMS

The primary aim of this study was to investigate survival in elderly patients with hip fracture and non-dialysis dependent CKD (eGFR <60 mL/min/1.73 m^2) compared to those with normal kidney function (eGFR ≥ 60 mL/min/1.73 m^2). We also investigated how demographic factors, co-morbidities and laboratory variables influenced mortality and length of stay.

2. Methods

2.1. Study design

This was a retrospective observational cohort study conducted at Changi General Hospital (CGH) with ethics approval from the Sing Health Institutional review board (2017/2962)

Study data was obtained from electronic medical records for patients >65 years of age admitted to CGH with hip fracture from June 1, 2014 to June 1, 2016.

2.1.1. Enrolment. Men and women >65 years of age, with hip fracture.

Hip fracture: Hip fracture in the elderly at Changi General Hospital is a part of a value care program where the evaluation and management is standardized. This pathway includes protocol on use of perioperative antibiotics as well as prevention of deep vein thrombosis.

2.1.2. Inclusion criteria. Patients with an established diagnosis of CKD as per the KDIGO guidelines.[13]

2.1.3. Exclusion criteria. Patients with no serum creatinine measurement within 3 months prior to admission and those with acute kidney injury and transient renal impairment were excluded.

Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation. Patients who did not undergo surgery for hip fracture and those who died during the index admission were excluded.

Patients were classified into 2 groups based on eGFR (mL/min/1.73 m^2):

1. CKD patients with eGFR <60 and
2. patients with normal kidney function, eGFR ≥ 60.

CKD patients were further stratified based on the KDIGO guidelines as follows: Stage 3a: eGFR 45–59, Stage 3b: eGFR 30–44, Stage 4: eGFR 15–29, Stage 5: eGFR <15.

2.1.4. Laboratory tests. The reference laboratory values for our hospital are: 25(OH) vitamin D, 30 to 100 ug/L; serum albumin, 37 to 51 G/L; HbA1C, 4.4% to 6.4% and serum phosphate 0.65 to 1.65 mmol/L.

2.1.5. Outcomes. The primary outcome measure in this study was mortality in elderly patients with hip fracture and non-dialysis dependent CKD versus those with normal kidney function. The time to death was measured from day of fracture to event. We also studied the effects of co-morbidity risk factors: cerebro vascular accident, peripheral vascular disease, cancer, diabetes mellitus, malignancy, chronic obstructive pulmonary disease, atrial fibrillation, ischemic heart disease, congestive heart failure and laboratory tests of haemoglobin, HBA1c, serum calcium, phosphorous and 25(OH) Vitamin D.

Additional outcome measures included length of stay in the 2 groups,

2.1.6. Follow up. All patients with hip fracture who underwent surgery were followed up from the index dates of June 2014 to 2016 to June 1st, 2018 or death.

2.1.7. Statistical methods. Continuous variables were summarized as mean $\pm$ SD or median (interquartile range) and categorical variables as proportions. Baseline comparisons between the CKD and No-CKD groups employed the two-sample *t*-test and the Wilcoxon rank sum test for continuous variables and Fisher exact test for categorical variables. We used univariate and multivariate Cox proportional hazards regression to investigate and identify risk factors associated with mortality among the demographic, comorbidity and laboratory variables collected. Variables significant at $P<.15$ in the univariate analysis were included as candidate predictors in a multivariable logistic regression analysis incorporating a stepwise selection algorithm (significance levels to enter and stay of 0.05 and 0.10, respectively) for the purpose of identifying a parsimonious subset of predictors of mortality. The Kaplan–Meier product-limit method and the log-rank test with posthoc multiple comparisons were used to obtain and statistically compare survival curves among 3 eGFR (mL/min/1.73 m^2) sub-classifications: eGFR <30, eGFR 30–59 and eGFR ≥ 60. All statistical analyzes were performed using SAS v9.4 (SAS Institute Inc., NC, USA). Statistical significance was set at $P<.05$.

2.2. Ethics statement

This retrospective study was approved by the Institutional Review Board of Sing Health, and informed consent was waived by the board.

A CONSORT chart describing study patient disposition is given in Figure 1. Among the 883 elderly patients who were admitted with hip fracture, 725 underwent surgery and were included in the study cohort. Nine had no eGFR data and so were excluded from the analysis.

Table 1 summarizes baseline demographic; clinical and laboratory variables results and comparisons between the 2 study groups: CKD (eGFR <60 mL/min/1.73 m^2) and non-CKD (≥ 60 mL/min/1.73 m^2). 46.6% (334/716) of patients were classified as CKD.

Mean age (years.) for CKD patients was 82.4 and 78.4 for non-CKD patients ($P<.0001$). 71.6% of CKD patients and 68.1% of non-CKD patients were female ($P=.329$). The only comorbidity to exhibit a difference between study groups was CCF (CKD, 2.10% vs non-CKD, 0.26%; $P=.029$). Laboratory tests resulting in significant differences between groups were Hb (CKD, $\bar{x}=11.8$

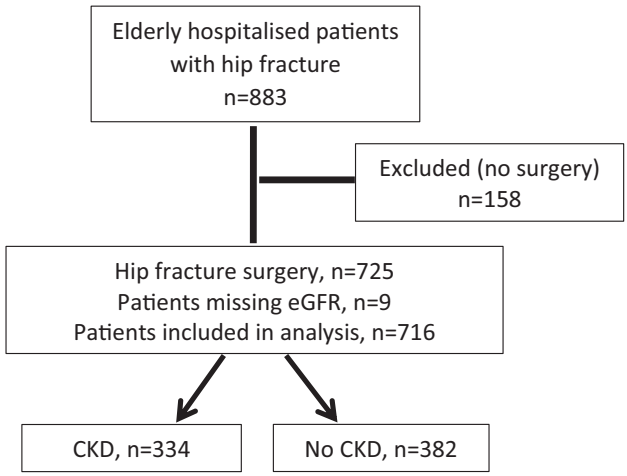

Figure 1. CONSORT chart for the analytic cohort.

vs non-CKD, $\bar{x} = 12.6$; $P < .0001$), serum phosphorous (CKD, median = 1.14 vs non-CKD, median = 1.10; $P = .001$) and length of stay (CKD, median = 10.0 vs non-CKD, median = 8.8; $P = .001$).

The mortality percentage in non-dialysis dependent CKD patients with hip fractures was 8.08% (27/334, 1021 pt-years) compared to 6.54% (25/382, 1055 pt-years) in patients with normal renal function.

2.3. Variables associated with mortality

2.3.1. Univariate logistic regression analysis. Cox proportional hazards univariate analysis resulted in the following variables showing significant association with mortality at $P < .05$: age (<80, ≥80 years.), gender (M/F), peripheral vascular disease (Y/N), malignancy (Y/N) and serum albumin (<30, ≥30 mg/dL) as statistically significant risk factors associated with mortality. The variables cerebrovascular accident (Y/N), eGFR (<30, 30–59, ≥60 mL/min/1.73 m^2) and Vitamin D (<30, ≥30 ug/L) were significant at $P < .05$ and as such were candidates for inclusion into the multivariable analysis incorporating a stepwise selection algorithm (Table 2).

2.3.2. Multivariable logistic regression analysis. Age (<80, ≥80 years.), gender (M/F) and serum albumin (<30, ≥30 mg/dL) selected by the stepwise selection algorithm as significant risk factors of mortality (all $P < .001$) (Table 3). Although statistically non-significant, eGFR (<30, 30–59, ≥60 mL/min/1.73 m^2) was included in the model as a known, clinically relevant risk factor associated with mortality in the elderly. The integrated time-dependent area under the 59, ≥ receiver operating characteristic (ROC) curve was IAUC = 0.718.

2.3.3. Kaplan–Meier survival analysis. Figure 2 shows Kaplan–Meier survival curves for the 3 eGFR level groups. In posthoc tests, a significant difference was found between the eGFR < 30 vs > 60 mL/min/1.73 m^2 group curves ($P = .047$). No significant differences were found in comparisons of the eGFR < 30 vs 30 to 59 mL/min/1.73 m^2 survival curves or the eGFR 30–59 vs > 60 mL/min/1.73 m^2 curves (both, $P > .05$) (Fig. 2).

3. Discussion

In this retrospective analysis cohort study of 716 patients, we examined the effect of non-dialysis dependent CKD on outcomes

Table 1

Baseline data summarized as n (%), mean ± SD, Median (IQR).

Variable	CKD (eGFR <60mL/min/1.73 m^2) (N = 334)	Non-CKD (eGFR ≥60mL/min/1.73 m^2) (N = 382)	P value[†]
Clinical characteristics			
Female gender	239 (71.6)	260 (68.1	.3286
Age (yrs)	82.4 ± 7.14	78.4 ± 7.37	<.0001
Co-morbidities			
CVA	27 (8.08)	28 (7.33)	.7789
PVD	3 (0.90)	4 (1.05)	1.0000
Cancer	26 (7.78)	26 (6.81)	.6661
Diabetes mellitus	148 (44.3)	178 (46.6)	.5482
COPD	7 (2.10)	8 (2.09)	1.0000
AF	4 (1.20)	2 (0.52)	. 4254
IHD	52 (15.6)	47 (12.3)	. 2328
CHF	7 (2.10)	1 (0.26)	.0285
Laboratory tests			
eGFR (mL/min/1.73 m^2)	41.9 ± 13.3	60.0 ± 0.26	<.0001
Hb (g/dL)	11.8 ± 1.85	12.6 ± 1.60	<.0001
Serum albumin (g/L)	36.2 ± 5.17	36.8 ± 4.95	.1176
HbA1C	6.50 ± 1.74	6.52 ± 1.63	.9250
Serum calcium (mmol/L)	2.25 ± 0.20	2.25 ± 0.14	.9636
Serum phosphorous (mmol/L)	1.14 (1.03, 1.29)	1.10 (0.97, 1.22)	.0008
Serum 25 (OH) D (ug/L)	24.3 ± 11.5	23.6 ± 11.6	.4519
Length of stay (days)	10.0 (7.56, 13.9)	8.82 (6.68, 12.6)	.0014
Days discharge to Event (death or last follow-up)	1051 (871, 1279)	1076 (886, 1321)	.1968

[†] Statistical tests: n (%), Fisher exact test; mean, 2-sample *t*-test; median, Wilcoxon rank-sum test.

Table 2

Cox proportional hazards univariate analysis of factors associated with mortality in the elderly with hip fracture.

Univariable analysis	HR (95% CI)	P value
Age: ≥80 yr vs <80 yr	2.40 (1.65, 3.51)	<.0001
Sex: Male vs Female	2.71 (1.93, 379)	<.0001
Diabetes mellitus: Yes/No	1.23 (0.88, 1.73)	.2221
Cerebrovascular accident: Yes/No	1.53 (0.92, 2.54)	.1037
COPD: Yes/No	1.56 (0.64, 3.82)	.3289
Peripheral vascular disease: Yes/No	3.16 (1.17, 8.55)	.0238
Malignancy: Yes/No	1.88 (1.13, 3.13)	.0149
eGFR: <30 mL/min vs ≥60 mL/min/1.73 m^2	1.69 (0.99, 2.89)	.0542
25 (OH) Vit D: <30 vs ≥30 ugl/L	0.71 (0.50, 1.02)	.0611
Serum albumin: <30 vs ≥30 G/L	2.80 (1.81, 4.33)	<.0001
HBa1C: <6 vs ≥6	0.93 (0.48, 1.78)	.8225
Serum Phosphate: <1.6 vs ≥1.6 mmol/L	1.52 (0.80, 2.91)	.2024

CI = confidence interval, COPD = chronic obstructive pulmonary disease, HR = hazard ratio.

Table 3

Cox proportional hazards model: Multivariable analysis of factors associated with mortality in elderly with hip fracture.

Variable	Hazard ratio	CI 95%	P value
Sex: Male	3.09	2.18, 4.38	<.0001
Age: ≥80 yrs	2.52	1.71, 3.80	<.0001
Serum Albumin <30 G/L	2.70	1.69, 4.13	<.0001
eGFR: 30–59 mL/min/1.73 m^2	0.80	0.80, 0.47	.4334
eGFR: ≥60 mL/min/1.73 m^2	0.77	0.46, 1.35	.3310

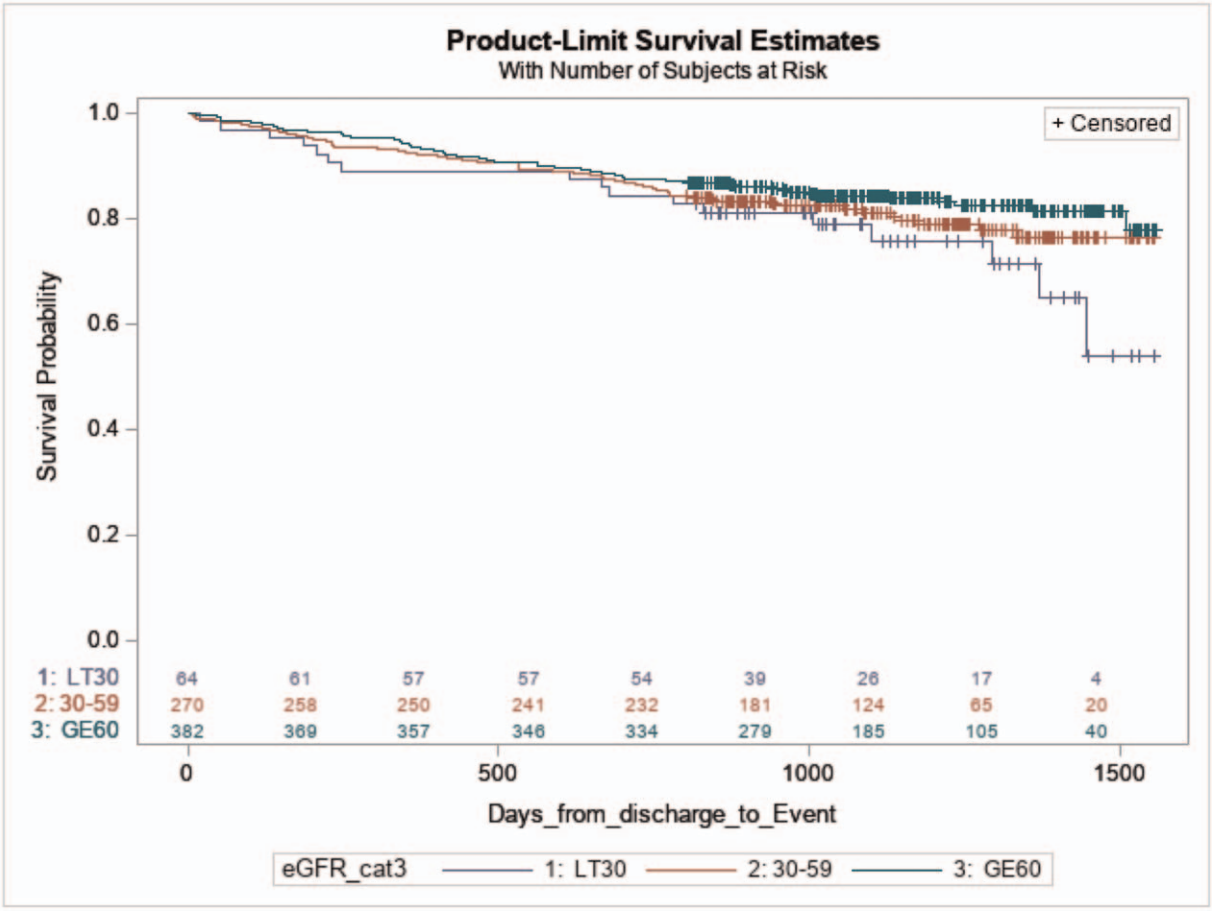

Figure 2. Kaplan–Meier Survival curves: (1) LT30: eGFR <30 mL/min/1.73 m^2, (2) 30–59: eGFR 30–59 mL/min/1.73 m^2, (3) GE60: eGFR ≥ 60 mL/min/1.73 m^2. Pair-wise comparisons among groups: (1) vs (2), $P=.840$; (1) vs (3), $P=.047$; (2) vs (3), $P=.216$.

in elderly patients with hip fracture. We found **male** sex, age greater than or equal to 80 years, low serum albumin and eGFR less than 30 mL/min/1.73 m^2 were associated with poor survival. The hospital stay in the CKD group was longer.

With an aging population worldwide, frailty in this group is not uncommon.[14] The associated cognitive dysfunction and morbidities make falls common. Chronic kidney disease also is more common in the elderly resulting in renal osteodystrophy, falls and resultant hip fractures.[15] In our cohort, male gender experienced poorer survival. A large population-based study from USA reported on a cohort of patients with hip fracture in the period 1985–2005 sourced from Medicare Provider Analysis Review (MEDPAR), found that a majority of hip fractures in men and women occurred in the age group 75 to 84 years. The percentage of those with hip fracture above 85 years of age increased from 38.0% (95% CI, 37.4%–38.5%) in 1986 to 43.6% (95% CI, 43.1%–44.1%) in 2005.[16] They reported that adjusted 360-day mortality was significantly higher in men.

We found that patients >80 years had poorer survival. Similar findings have been reported by an Australian veterans database.[17] Another population-based study from Minnesota, comparing 312 elderly patients with hip fracture and 312 controls, reported mortality of 20% in the hip fracture group compared to 11% for non-hip fractures. Functional decline was significant in the hip fracture group with 64% admitted to a nursing home in the first year against 7% in the controls.[18]

Low serum albumin is commonly associated with hip fracture in the elderly, 61% to 81.2%.[19,20] In a Spanish study of 509 patients with a mean age of 85 years, 409(81.2%) had protein malnutrition.[19] A prospective randomized controlled study from Sweden demonstrated nutritional supplementation whilst in-hospital in a cohort of 80 patients with hip fracture, mean age of 78 years resulted in a reduction in fracture related complications from 70% (control group) to 15% (intervention group) over a follow up period of 120 days.[20] We found low serum albumin, <30G/L had a HR 2.697 (95% CI, 1.691–4.127) for risk of mortality (Table 3). A population based prospective study of 472 consecutive patients >65 years of age with hip fracture reported higher risk of mortality in those with malnutrition, and reported a HR of 2.16 (95% CI, 1.07–4.34)—similar to our study.[21]

End stage renal disease is exacerbated by hip fractures and results in poorer survival. A study using data from the United States Renal Data Systems for years 1995 to 2000, compared 7636 patients on dialysis with hip fracture to a matched cohort of 22,896. The relative risk of mortality in the dialysis cohort was 1.99 (95% CI, 1.91,2.07, $P<.001$).[9] A study from Taiwan similarly compared mortality in 997 dialysis patients with hip fracture with 4985 hip fracture without dialysis from their National insurance database followed up over 10 years.[7] In the dialysis group, hazard ratios for mortality (95% CI) at 3 months, 1 year, 1 to 6 years and 6 to 10 years were 2.95 (2.48–3.51), 2.84

(2.55–3.15), and 2.39 (1.94–2.93). The non-dialysis group did consistently better over the 10-year period (0–10 years, Log-Rank test, $P < .001$).

Nikolas et al in an analysis of the NHANES III survey found increased likelihood of hip fracture in patients with CKD and eGFR < 60 mL/min (OR 2.12, 95%CI, 1.18–3.80).[11] The effect of non-dialysis dependent CKD (Stage 3–5) on survival with hip fractures is not well studied. We found eGFR < 30 mL/min/1.73 m^2 was significantly associated with mortality in univariable analysis, and the Kaplan–Meier survival curve comparing eGFR < 30 mL/min vs >60 mL/min/1.73 m^2 showed poorer survival ($P < .047$). We also observed that there was no difference in the mortality of the 2 groups till almost 2 years from discharge, Figure 2. Not dissimilar to our findings, a study from Newcastle reported on 566 patients elderly patients with hip fracture and non- dialysis dependent renal dysfunction were at greatest risk of mortality.[10]

3.1. Strengths and limitations

The strengths of our study included a relatively large patient group (716 patients) and the availability of data on co-morbid conditions. Mortality was investigated through comparison with elderly hip fracture patients without CKD.

Limitations of our study are the retrospective design and very few cases with CKD 5. In addition, selection bias could not be excluded in the non-CKD group even though multivariate analysis with baseline demographics, laboratory parameters as well as a comprehensive list of comorbidities was used.

4. Conclusion

In summary, in elderly, non-dialysis dependent CKD patient with hip fracture we found that male gender, age ≥80 years, low serum albumin and eGFR < 30 mL/min/1.73 m^2 were associated with higher risk of death. The hospital stay in the CKD group was also longer. Additional studies are needed to validate our findings.

Author contributions

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