Hindawi
International Journal of Clinical Practice
Volume 2024, Article ID 4456803, 26 pages
https://doi.org/10.1155/2024/4456803

*Research Article*

# Chronic Kidney Disease in Patients with Hip Fracture: Prevalence and Outcomes

**Alexander Fisher**[1,2,3] **Jo-Wai Douglas Wang**[1,3] **and Paul N. Smith**[2,3]

[1]*Department of Geriatric Medicine, The Canberra Hospital, Canberra 2614, Australia*
[2]*Department of Orthopaedic Surgery, The Canberra Hospital, Canberra 2614, Australia*
[3]*Australian National University Medical School, Canberra 2614, Australia*

Correspondence should be addressed to Alexander Fisher; alex.fisher@act.gov.au

Received 23 September 2023; Revised 20 February 2024; Accepted 10 April 2024; Published 9 May 2024

Academic Editor: Okan Aslantürk



*Objective*. Although the association between chronic kidney disease (CKD) and osteoporotic fractures is well established, data on CKD combined with hip fracture (HF) are scarce and controversial. We aimed to assess in patients with HF the prevalence of CKD, its impact on hospital mortality and length of stay (LOS) and to determine the prognostic value of CKD to predict hospital outcomes. *Methods*. Prospectively collected clinical data were analysed in 3623 consecutive HF patients aged ≥65 years (mean age 83.4 ± 7.50 [standard deviation] years; 74.4% females). *Results*. CKD among older patients with HF is highly prevalent (39.9%), has different clinical characteristics, a 2.5-fold higher mortality rate, and 40% greater risk of prolonged LOS. The strongest risk for a poor outcome was advanced age (>80 years). The risk of death substantially increases in combination with chronic disorders, especially coronary artery disease, anaemia, hyperparathyroidism, and atrial fibrillation; models based only on three variables—CKD stage, age >80, and presence of a specific chronic condition—predicted in-hospital death with good discrimination capability (AUC ≥ 0.700) and reasonable accuracy, the number needed to predict ranged between 5.7 and 14.5. Only 12% of HF patients received osteoporotic drugs prefracture. *Conclusion*. In HF patients with CKD, the risk of adverse outcomes largely increases in parallel with worsening kidney function and, especially, in combination with comorbidities; models based on three admission variables predict a fatal outcome. Assessment of renal function is essential to preventing osteoporotic fractures.

## 1. Introduction

Both chronic kidney disease (CKD) and osteoporotic hip fractures (HF) are major and steadily rising public health problems globally, affecting 843.6 [1, 2] and 14.2 [3] (4.5 million people with HF per year worldwide [4]) million individuals, respectively, and contributing to high morbidity, mortality, and excess health and social care costs [5–12]. Both pathologies are bidirectionally interrelated: CKD compromises bone-mineral status and predisposes to falls and vice versa [7, 13–16].

Although kidney-related mechanisms involved in maintenance of musculoskeletal health [14, 17–21] have been intensively researched for decades and the association between CKD and osteoporotic fractures (OF) is well established [22, 23], studies on CKD combined with HF, the most devastating complication of osteoporosis (OP), are relatively rare [13, 24, 25]. The relationship between kidney function and postoperative outcomes in hip fracture (HF) patients has not been systematically investigated, and the few studies that evaluated the input of CKD on HF outcomes have yielded conflicting results [25–29]. Despite the great interest in predicting the risk of fracture and identifying people who will benefit from therapeutic interventions, data on the use, effectiveness, and safety of anti-osteoporotic drugs in patients with different stages of CKD is also scarce and uncertain [9, 12, 30–36]. Therefore, in this study, we aimed to assess the prevalence of CKD among patients with HF (compared to the general population) and the impact of CKD on HF outcomes (hospital mortality and length of stay [LOS]) with the

inclusion of additional effects of age, gender, degree of renal dysfunction, and comorbidities. We hypothesised that higher CKD stages and specific clinical characteristics could be associated with increased post-operative mortality and LOS and may be used for prognostication of adverse outcomes.

## 2. Materials and Methods

*2.1. Patients.* In a total of 3623 consecutive patients aged 65 years or older admitted with a low-energy traumatic (i.e., related to an accidental fall while walking or standing) nonpathological HF except for osteoporosis (categorised as either cervical or trochanteric) to the Department of Orthopaedic Surgery of the Canberra Hospital (tertiary university centre) between 2000 and 2019 and had operative fracture treatment were included in the study. Patients with medium- or high-energy fractures (e.g., major trauma, car accident, fall from height, etc.), pathological fractures (due to bone malignant tumour or metastasis), subtrochanteric, multiple fractures, or polytrauma, and those who were under the age of 65 were excluded. The mean age of patients was 83.4 ± 7.50 [SD] years (median age was 84 years [interquartile range 10]), 75.3% were women, and 52.6% had a femoral cervical fracture. All patients followed a similar postoperative protocol with mobilisation out of bed on day one and urinary catheter out on day two.

*2.2. Data Collection and Variables.* Prefracture hospital and general practitioners' medical case records were reviewed, data on fracture type (cervical or trochanteric), sociodemographic features (including residency in a permanent care facility (PRCF), use of walking aids), lifestyle factors (smoking status, alcohol use), chronic comorbidities (including hypertension, anaemia, history of coronary artery disease (CAD), history of acute myocardial infarction (MI), atrial fibrillation (AF), type 2 diabetes mellitus (T2DM), cerebrovascular accident (CVA), transient ischaemic attack (TIA), chronic obstructive pulmonary disease (COPD), dementia, Parkinson's disease (PD)), medication profile (including active osteoporosis therapy at the time of admission), routine laboratory parameters and hospital outcomes (death, LOS) were prospectively recorded and analysed.

*2.3. Definitions*

*2.3.1. Renal Function Evaluation and CKD Stratification.* CKD was defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 $m^2$ (calculated by the CKD-EPI equation) [37]. CKD stages were defined according to eGFR (ml/min/1.73 $m^2$) as follows: no CKD or G1 (eGFR > 90), G2 (eGFR 60–89), G3a (eGFR 45–59), G3b (eGFR 30 to 44), G4 (eGFR 15–29), G5 (eGFR ≤ 14). The evaluation of the effect of CKD on mortality and LOS involved two steps. Initially, those with moderate or severe CKD (CKD G3-5; eGFR ≤ 60 ml/min/1.73 $m^2$) were collectively compared to patients with mild or no CKD (G1-2; eGFR > 60 ml/min/1.73 $m^2$) as the reference. Subsequently, CKD G3, G4, and G5 were each compared separately to the CKD G1-2 group.

The prevalence of CKD among the HF patients was compared to that in the general population (matched by age and gender), using data obtained from the Australian Bureau of Statistics, Australian Health of Institute and Welfare [38–40]. The prevalences of morbidities, and the mortality rates in the CKD and non-CKD groups were compared.

Anaemia was defined as haemoglobin level <130 g/L in men and <120 g/L in women. Vitamin D deficiency was defined as 25 (OH) D ≤25 nmol/L and hypovitaminosis D/insufficiency as ≤50 nmol/L, hyperparathyroidism was defined as elevated serum PTH (>6.8 pmol/L, the upper limit of the laboratory reference range).

*2.4. Statistical Analyses.* Continuous variables were reported as median and interquartile range (IQR) or as means ± standard deviations (SD), based on their distribution, while categorical variables were reported as absolute numbers and percentages. Comparisons between groups for continuous variables were performed using Student's *t*-test (if data were normally distributed) or Mann–Whitney *U* test; $\chi^2$ test (Yates corrected) was applied for categorical variables. Univariate and multivariate logistic regression analyses were used to determine the odds ratio (OR) and 95% confidence intervals (CI) for associations between an outcome (dependent variable) and different clinical and laboratory variables; all potentially confounding variables with a statistical significance ≤0.15 on univariate analyses were included in the final multivariate analyses. CKD stages, defined by preoperative eGFR levels, and comorbidities were input into the models as categorical variables.

Poisson regression models were used to determine the specific influence of age (>80 years), gender and main comorbidities on the association between CKD and HF outcomes; results were reported as incidence rate ratios (IRR) with 95% CI.

To evaluate the ability of specific clinical parameters (single and combined) to predict postoperative outcomes receiver-operating characteristic (ROC) curve analyses (the area under the ROC curve, AUC) were performed. Sensitivity, specificity, accuracy, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LP+), negative likelihood ratio (LP-) and number of patients needed to be examined for correct prediction (NNP-[41, 42]) were calculated to assess the discriminatory performance of each condition or model. The predictive performance of the tests was further assessed for calibration using the Hosmer-Lemeshow goodness-of-fit test [43]. All tests were two-tailed; $p$ values <0.05 were considered statistically significant.

Analyses were conducted using Python (v3.8.10), the NumPy, SciPy and pandas packages [44–46]; as well as the R statistical software (v4.2.1) [47].

## 3. Results

*3.1. Patient Characteristics.* The main sociodemographic and clinical characteristics as well as hospital outcomes of the study population according to CKD presence or absence are

displayed in Table 1. Of 3623 HF patients in our cohort, 2179 (60.1%) had eGFR > 60 ml/min/1.73 $m^2$ and were considered non-CKD, while 1444 (39.9%) individuals had CKD stages 3-5; in both groups about 3/4 were females. The more prevalent age group was >80 years. The CKD group was significantly older (80.1% were aged >80 years vs. 59.7% among the non-CKD), had a higher proportion of permanent residential care facilities (PRCF) residents (+6.5%) and walking aids users (+5.9%), but fewer current smokers (−3.4%) and alcohol over-users (>3 times a week, −2.3%). The trochanteric HF type was more common among CKD patients (+4.6%). The CKD group, compared to the non-CKD, demonstrated, unsurprisingly, a significantly greater prevalence of anaemia (+15.0%), CAD (+12.2%), hypertension (+9.5%), T2DM (+6.4%), AF (+6.2%), prior AMI (+4.0%), CVA/TIA (+2.8%), dementia (+3.8%), hyperparathyroidism (+21.0%), and a lower proportion of individuals with Parkinson's disease (PD, −3.3%). The prevalence of COPD, malignancy, and vitamin D deficiency/insufficiency did not differ between these two groups; preoperatively HF patients, especially those with CKD, were rarely diagnosed with osteoporosis (11.8% vs. 14.0%, $p = 0.062$).

The proportion of patients with multiple chronic conditions (in addition to CKD) in the CKD group was significantly higher than in the rest of the cohort: no comorbid diseases were found in 1.9% vs. 3.3%, respectively ($p < 0.019$), one comorbidity in 5.1% vs. 12.0% ($p < 0.001$), two comorbidities in 13.6% vs. 22.8% ($p < 0.001$), three or more comorbidities in 79.4% vs. 62.0% ($p < 0.001$); in the CKD group the highest percentage of patients with multimorbidity (≥3) was observed among patients aged >80 years (80.5% vs. 74.7%, $p = 0.033$).

Stratifying by CKD stage (Table 2) showed that in the group with eGFR < 60 ml/min, half (716, 49.6%) had stage 3a, 465 (32.2%) had stage 3b, 217 (15.0%) had stage 4, and 46 (3.2%) had stage 5 disease. Compared to the group with eGFR > 60 ml/min, patients with CKD stages G3-G4 were significantly older (median age +3-4 years); about 3/4 of them were women, while those with CKD stage 5 were younger (−3 years); and more than half (52.2%) were men. Higher CKD stages were associated with increased proportion of subjects with a trochanteric fracture (statistically significant only in stage 4), walking aids users (except stage 5), PRCF residents (significant in stage 3), lower proportions of current smokers (in stages 3-4) and alcohol over-users (stage 3a and 3b). Unsurprisingly, with higher CKD stages there was a significantly increased proportion of patients with comorbidities including hypertension (52.6% in stages 1-2 vs. 78.3% in stage 5), anaemia (36.3% vs. 76.1%, respectively), CAD (24.7% vs. 63.0%, respectively), history of MI (6.3% vs. 23.9%, respectively), T2DM (10.7% vs. 34.8%, respectively), hyperparathyroidism (38.1% vs. 84.8%, respectively), and AF (16.9% vs. 28.1%, in stage 4), whereas there was a lower percentage of subjects with PD (6.1% vs. 1.4% in stage 4); in patients with CKD G3a a significantly higher proportion of patients had dementia (36.0% vs. 29.3%) and a history of CVA/TIA (21.4% vs. 17.6%). The prevalence of patients with COPD, history of malignant disease, pre-HF diagnosis of OP (except in those with G4 disease) as well as with vitamin D deficiency in the CKD G3-5 groups was similar to that in subjects with CKD G1-2 (except higher prevalence of vitamin D insufficiency among the CKD G3b group).

Pre-HF, osteoporotic drugs in general were rarely prescribed, and even less frequently so to patients with CKD. The difference between the CKD and non-CKD groups was of borderline significance regarding bisphosphonates (8.9% and 10.9%, respectively, $p = 0.059$); in CKD G4 and G5 groups only 6.0% ($p = 0.032$) and 6.5% of patients, respectively, have been treated with a bisphosphonate; denosumab (1.6% and 2.0%, respectively), calcium supplements (17.2% and 17.1%, respectively), and cholecalciferol (31.2% and 28.9%) usage rates were similar (except for a higher prescription of cholecalciferol to CKD G5 (47.8%, $p = 0.008$); among the minority of HF patients treated with calcitriol the proportion of subjects with CKD was higher (3.0% vs. 1.1%, $p < 0.001$).

In summary, HF patients with a reduced eGFR, as compared with the group with an eGFR of ≥60 ml/min/1.73 $m^2$, were older and had a higher prevalence of anaemia, cardio- and cerebrovascular diseases (hypertension, CAD, AF, prior AMI, CVA/TIA), T2DM, dementia and hyperparathyroidism, with an increase of the prevalence of these comorbid conditions in parallel with CKD progression (from stage 3 to 5). Pre-HF the CKD patients were rarely diagnosed with and treated for OP.

*3.2. CKD Prevalence among HF Patients and in the General Population.* In the total Australian population, the prevalence of CKD (stages >3) was estimated to be 3.6% [38]—3.4% [39, 40] (similar rates in men and women) which increased with age: 2.4% for people aged 65–74 years and 4.6% for people aged 75 years and over [40]. The most recently available data on percentage of Australians with CKD (G3-5) in the total population is 4.6% (4.2% among non-Aboriginal and Torres Strait Islander people) [48]. These data indicate that among HF patients aged ≥65 years, the prevalence of CKD (G3-5) is more than 9-times higher compared to the total Australian population of the same age (39.9% vs. 3.6%–4.6%).

*3.3. CKD and Short-Term Hospital Outcomes*

*3.3.1. Mortality.* In our HF cohort, the total all-cause in-hospital postoperative mortality rate was 5.2% (Table 1). Among the 189 HF patients who died in the hospital, 118 (62.4%) had CKD, making CKD the most prevalent comorbidity associated with a fatal outcome. Among the CKD patients with a lethal outcome 42 (35.6%) subjects were in stage 3a, 38 (32.2%) were in stage 3b, 29 (24.6%) were in stage 4 and 9 (7.6%) were in stage 5. In the total HF cohort, a decrease in eGFR of 1 ml/min/1.73 $m^2$ increased mortality risk by 3% (OR 1.03, 95% CI 1.02–1.04, $p < 0.001$). Patients with HF and CKD compared to subjects without CKD had a 2.6-times higher mortality rate (8.2% vs. 3.3%, OR 2.64, 95% CI 1.95–3.58, $p < 0.001$). Among all fatalities 82.0%

Table 1: Sociodemographic and clinical characteristics and hospital outcomes in elderly (aged ≥65 years) patients with osteoporotic hip fracture with and without chronic kidney disease (CKD).

| Variable | Total cohort ($n = 3623$) | With CKD ($n = 1444$, 39.9%) | Without CKD ($n = 2179$, 60.1%) | $p$ value |
|---|---|---|---|---|
| Age, years, median (IQR) | 84 (10) | 86 (9) | 83 (10) | <0.001 |
| Aged 65–79 years, *n* (%) | 1167 (32.2) | 288 (19.9) | 879 (40.3) | <0.001 |
| Aged >80 years, *n* (%) | 2456 (67.8) | 1156 (80.1) | 1300 (59.7) | <0.001 |
| Females, *n* (%) | 2728 (75.3) | 1106 (76.6) | 1622 (74.4) | 0.152 |
| PRCF resident, *n* (%) | 1207 (33.3) | 537 (37.2) | 670 (30.7) | <0.001 |
| Smoker (active), *n* (%) | 180 (5.0) | 42 (2.9) | 138 (6.3) | <0.001 |
| Ex-smoker (active), *n* (%) | 450 (12.4) | 180 (12.5) | 270 (12.4) | 0.982 |
| Alcohol over-user*, *n* (%) | 144 (4.0) | 38 (2.6) | 106 (4.9) | 0.001 |
| Walking aids user, *n* (%) | 1299 (35.9) | 568 (39.4) | 731 (33.5) | <0.001 |
| Fracture type [Tr], *n* (%) | 1719 (47.4) | 725 (50.2) | 994 (45.6) | 0.007 |
| Hypertension, *n* (%) | 2044 (56.4) | 897 (62.1) | 1147 (52.6) | <0.001 |
| Anaemia, *n* (%) | 1531 (42.2) | 741 (51.3) | 790 (36.3) | <0.001 |
| CAD, *n* (%) | 1072 (29.6) | 533 (36.9) | 539 (24.7) | <0.001 |
| History of AMI, *n* (%) | 286 (7.9) | 149 (10.3) | 137 (6.3) | <0.001 |
| AF, *n* (%) | 702 (19.4) | 333 (23.1) | 369 (16.9) | <0.001 |
| T2DM, *n* (%) | 481 (13.3) | 247 (17.1) | 234 (10.7) | <0.001 |
| COPD, *n* (%) | 560 (15.5) | 217 (15.0) | 343 (15.7) | 0.599 |
| Dementia, *n* (%) | 1116 (30.8) | 478 (33.1) | 638 (29.3) | 0.016 |
| OP, *n* (%) | 477 (13.2) | 171 (11.8) | 306 (14.0) | 0.062 |
| CVA/TIA, *n* (%) | 678 (18.7) | 294 (20.4) | 384 (17.6) | 0.043 |
| PD, *n* (%) | 172 (4.7) | 40 (2.8) | 132 (6.1) | <0.001 |
| Malignancy, *n* (%) | 82 (2.3) | 34 (2.4) | 48 (2.2) | 0.852 |
| PTH > 6.8 pmol/L | 1684 (46.5) | 854 (59.1) | 830 (38.1) | <0.001 |
| 25 (OH) vitamin D ≤25 nmol/L, *n* (%) | 610 (16.8) | 255 (17.7) | 355 (16.3) | 0.302 |
| 25 (OH) vitamin D ≤50 nmol/L, *n* (%) | 1659 (45.8) | 675 (46.7) | 984 (45.2) | 0.366 |
| *Usage of anti-osteoporotic medications* | | | | |
| Bisphosphonate, *n* (%) | 367 (10.1) | 129 (8.9) | 238 (10.9) | 0.059 |
| Denosumab, *n* (%) | 66 (1.8) | 23 (1.6) | 43 (2.0) | 0.477 |
| Caltrate, *n* (%) | 622 (17.2) | 249 (17.2) | 373 (17.1) | 0.957 |
| Cholecalciferol, *n* (%) | 1080 (29.8) | 451 (31.2) | 629 (28.9) | 0.137 |
| Calcitriol, *n* (%) | 66 (1.8) | 43 (3.0) | 23 (1.1) | <0.001 |
| *Outcomes* | | | | |
| Died: | | | | |
| Total, *n* (%) | 189 (5.2) | 118 (8.2) | 71 (3.3) | <0.001 |
| Females, *n* (%) | 130 (4.8) | 83 (7.5) | 47 (2.9) | <0.001 |
| Males, *n* (%)[(3)] | 59 (6.6) | 35 (10.4) | 24 (4.3) | 0.003 |
| Aged >80 years, *n* (%) | 155 (6.3) | 100 (8.7) | 55 (4.2) | <0.001 |
| Aged ≤80 years, *n* (%) | 34 (2.9) | 18 (6.3) | 16 (1.8) | 0.165 |
| LOS, days | | | | |
| Total cohort: | | | | |
| >10, *n* (%) | 2053 (56.7) | 871 (60.3) | 1182 (54.2) | <0.001 |
| 10–20, *n* (%) | 1214 (33.5) | 488 (33.8) | 726 (33.3) | 0.793 |
| >20, *n* (%) | 839 (23.2) | 383 (26.5) | 456 (20.9) | <0.001 |
| Non-PRCF residents: | Total ($n = 2416$) | CKD ($n = 907$, 37.5%) | No CKD ($n = 1509$, 62.5%) | |
| >10, *n* (%) | 1543 (63.9) | 623 (68.7) | 920 (61.0) | <0.001 |
| 10–20, *n* (%) | 874 (36.2) | 331 (36.5) | 543 (36.0) | 0.835 |
| >20, *n* (%) | 669 (27.7) | 292 (32.2) | 377 (25.0) | <0.001 |

$p$ value: Mann-Whitney $U$ test for continuous variables (age), Pearson's Chi-square test (Yates corrected) for categorical variables. Abbreviations: IQR, interquartile range; CKD, chronic kidney disease (estimated glomerular filtration rate <60 mL/min/1.73 m$^2$); CAD, coronary artery disease; AMI, acute myocardial infarction; AF, atrial fibrillation; T2DM, type 2 diabetes mellitus; COPD, chronic obstructive pulmonary disease; PD, Parkinson's disease; CVA, cerebrovascular accident (stroke); TIA, transient ischaemic attack; Tr, trochanteric fractures; PRCF, permanent residential care facility; PTH, parathyroid hormone; OP, osteoporosis; LOS, length of hospital stay; *> 3 times a week.

were aged >80 years with a 2.2-times higher mortality rate (6.3% vs. 2.9%, Table 1). In the CKD group the corresponding figures were 84.7% and 1.4 (8.7% vs. 6.3%). In the non-CKD group, 77.5% of fatalities were also among the >80 years old, constituting 37.6% (71/189) of all deaths and the mortality rate was 2.3-times higher than in the aged <80 years (4.2% vs. 1.8%, Table 1).

There were also gender differences in the fatal outcome incidence. Females represented 75.3% of the entire HF cohort and were also more prevalent across CKD stage 3-4.

Table 2: Characteristics of patients with hip fracture and chronic kidney disease (CKD) by CKD stage, age, gender, fracture type, comorbidities, and hospital outcomes.

| Variable | Renal status (CKD) | | | | | *p* value | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Stage G1-2 [1] ($n = 2179$, –/60.1%**) | Stage G3a [2] ($n = 716$, 19.8%/49.6%**) | Stage G3b [3] ($n = 465$, 12.8%/32.2%**) | Stage G4 [4] ($n = 217$, 6.0%/15.0%**) | Stage G5 [5] ($n = 46$, 1.3%/3.2%**) | $p_{2-1}$ | $p_{3-1}$ | $p_{4-1}$ | $p_{5-1}$ | $p_{4-2}$ |
| Age, years, median (IQR) | 83 (10) | 86 (8) | 87 (8) | 86 (9) | 80 (15) | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| Aged 65–79 years, *n* (%) | 879 (40.3) | 150 (20.9) | 74 (15.9) | 39 (18.0) | 25 (54.3) | <0.001 | <0.001 | <0.001 | 0.078 | 0.390 |
| Aged >80, *n* (%) | 1300 (59.7) | 566 (79.1) | 391 (84.1) | 178 (82.0) | 21 (45.7) | <0.001 | <0.001 | <0.001 | 0.078 | 0.390 |
| Females, *n* (%) | 1622 (74.4) | 567 (79.2) | 360 (77.4) | 157 (72.4) | 22 (47.8) | 0.012 | 0.198 | 0.556 | <0.001 | 0.043 |
| Fracture type [Tr], *n* (%) | 994 (45.6) | 348 (48.6) | 234 (50.3) | 117 (53.9) | 26 (56.5) | 0.178 | 0.073 | 0.023 | 0.187 | 0.196 |
| PRCF resident, *n* (%) | 670 (30.7) | 290 (40.5) | 160 (34.4) | 77 (35.5) | 10 (21.7) | <0.001 | 0.136 | 0.174 | 0.250 | 0.213 |
| Smoker (active), *n* (%) | 138 (6.3) | 23 (3.2) | 15 (3.2) | 3 (1.4) | 1 (2.2) | 0.002 | 0.013 | 0.005 | 0.398 | 0.230 |
| Ex-smoker, *n* (%) | 270 (12.4) | 90 (12.6) | 47 (10.1) | 35 (16.1) | 8 (17.4) | 0.952 | 0.200 | 0.142 | 0.430 | 0.217 |
| Alcohol over-use*, *n* (%) (4) | 106 (4.9) | 17 (2.4) | 12 (2.6) | 7 (3.2) | 2 (4.3) | 0.006 | 0.042 | 0.359 | 1.000 | 0.653 |
| Walking aids user, *n* (%) | 731 (33.5) | 277 (38.7) | 188 (40.5) | 86 (39.6) | 17 (37.0) | 0.014 | 0.005 | 0.084 | 0.744 | 0.865 |
| Hypertension, *n* (%) | 1147 (52.6) | 430 (60.1) | 284 (61.1) | 147 (67.7) | 36 (78.3) | 0.001 | 0.001 | <0.001 | 0.001 | 0.050 |
| Anaemia, *n* (%) | 790 (36.3) | 314 (43.9) | 247 (53.1) | 145 (66.8) | 35 (76.1) | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| CAD, *n* (%) | 539 (24.7) | 212 (29.6) | 185 (39.9) | 107 (49.3) | 29 (63.0) | 0.011 | <0.001 | <0.001 | <0.001 | <0.001 |
| History of AMI, *n* (%) | 137 (6.3) | 63 (8.8) | 37 (8.0) | 38 (17.5) | 11 (23.9) | 0.027 | 0.220 | <0.001 | <0.001 | <0.001 |
| AF, *n* (%) | 369 (16.9) | 156 (21.8) | 104 (22.4) | 61 (28.1) | 12 (26.1) | 0.004 | 0.007 | <0.001 | 0.152 | 0.066 |
| T2DM, *n* (%) | 234 (10.7) | 100 (14.0) | 74 (15.9) | 57 (26.3) | 16 (34.8) | 0.023 | 0.002 | <0.001 | <0.001 | <0.001 |
| COPD, *n* (%) | 343 (15.7) | 96 (13.4) | 75 (16.2) | 38 (17.5) | 8 (17.4) | 0.147 | 0.876 | 0.560 | 0.921 | 0.162 |
| Dementia, *n* (%) | 638 (29.3) | 258 (36.0) | 147 (31.7) | 66 (30.4) | 7 (15.2) | 0.001 | 0.331 | 0.786 | 0.055 | 0.149 |
| OP, *n* (%) | 306 (14.0) | 97 (13.5) | 53 (11.4) | 18 (8.3) | 3 (6.5) | 0.787 | 0.151 | 0.024 | 0.213 | 0.052 |
| CVA/TIA, *n* (%) | 384 (17.6) | 153 (21.4) | 84 (18.1) | 49 (22.6) | 8 (17.4) | 0.029 | 0.873 | 0.086 | 1.000 | 0.775 |
| PD, *n* (%) | 132 (6.1) | 27 (3.8) | 8 (1.7) | 3 (1.4) | 2 (4.3) | 0.025 | <0.001 | 0.007 | 0.866 | 0.127 |
| Malignancy, *n* (%) | 48 (2.2) | 14 (2.0) | 15 (3.2) | 4 (1.8) | 1 (2.2) | 0.804 | 0.252 | 0.918 | 1.000 | 1.000 |
| PTH > 6.8 pmol/L, *n* (%) | 830 (38.1) | 350 (48.9) | 300 (64.5) | 165 (76.0) | 39 (84.8) | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| 25 (OH) vitamin D ≤25 nmol/L, *n* (%) | 355 (16.3) | 119 (16.6) | 92 (19.8) | 37 (17.1) | 7 (15.2) | 0.883 | 0.079 | 0.848 | 1.000 | 0.964 |
| 25 (OH) vitamin D ≤50 nmol/L, *n* (%) | 984 (45.2) | 307 (42.9) | 237 (51.0) | 111 (51.2) | 20 (43.5) | 0.307 | 0.026 | 0.105 | 0.939 | 0.039 |
| *Usage of anti-osteoporotic medications* | | | | | | | | | | |
| Bisphosphonate, *n* (%) | 238 (10.9) | 71 (9.9) | 42 (9.0) | 13 (6.0) | 3 (6.5) | 0.492 | 0.263 | 0.032 | 0.477 | 0.102 |
| Denosumab, *n* (%) | 43 (2.0) | 14 (2.0) | 8 (1.7) | 1 (0.5) | 0 (0.0) | 1.000 | 0.862 | 0.188 | 0.674 | 0.220 |
| Caltrate, *n* (%) | 373 (17.1) | 126 (17.6) | 78 (16.8) | 32 (14.7) | 13 (28.3) | 0.812 | 0.912 | 0.427 | 0.075 | 0.380 |
| Cholecalciferol, *n* (%) | 629 (28.9) | 229 (32.0) | 138 (29.7) | 62 (28.6) | 22 (47.8) | 0.124 | 0.769 | 0.990 | 0.008 | 0.386 |
| Calcitriol, *n* (%) | 23 (1.1) | 14 (2.0) | 15 (3.2) | 6 (2.8) | 8 (17.4) | 0.095 | 0.001 | 0.061 | <0.001 | 0.650 |

Table 2: Continued.

| Variable | Renal status (CKD) | | | | | $p$ value | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Stage G1-2 [1] ($n = 2179$, −/60.1%**) | Stage G3a [2] ($n = 716$, 19.8%/49.6%**) | Stage G3b [3] ($n = 465$, 12.8%/32.2%**) | Stage G4 [4] ($n = 217$, 6.0%/15.0%**) | Stage G5 [5] ($n = 46$, 1.3%/3.2%**) | $p_{2-1}$ | $p_{3-1}$ | $p_{4-1}$ | $p_{5-1}$ | $p_{4-2}$ |
| *Outcomes* | | | | | | | | | | |
| Died | | | | | | | | | | |
| Total, *n* (%) | 71 (3.3) | 42 (5.9) | 38 (8.2) | 29 (13.4) | 9 (19.6) | 0.003 | <0.001 | <0.001 | <0.001 | <0.001 |
| Females, *n* (%) | 47 (2.9) | 29 (5.1) | 28 (7.8) | 21 (13.4) | 5 (22.7) | 0.009 | <0.001 | <0.001 | 0.001 | 0.002 |
| Males, *n* (%) | 24 (4.3) | 13 (8.7) | 10 (9.5) | 8 (13.3) | 4 (16.7) | 0.199 | 0.110 | 0.004 | <0.001 | 0.172 |
| Aged >80 years, *n* (%) | 55 (4.2) | 38 (6.7) | 31 (7.9) | 25 (14.0) | 6 (28.6) | <0.001 | <0.001 | <0.001 | <0.001 | 0.002 |
| Aged ≤80 years, *n* (%) | 16 (1.8) | 4 (2.7) | 7 (9.5) | 4 (10.3) | 3 (12.0) | 0.816 | 0.177 | 0.186 | 0.001 | 0.168 |
| LOS, days | | | | | | | | | | |
| Total cohort: | | | | | | | | | | |
| >10, *n* (%) | 1182 (54.2) | 416 (58.1) | 288 (61.9) | 132 (60.8) | 35 (76.1) | 0.079 | 0.003 | 0.074 | 0.005 | 0.524 |
| >20, *n* (%) | 456 (20.9) | 166 (23.2) | 136 (29.2) | 61 (28.1) | 20 (43.5) | 0.221 | <0.001 | 0.018 | <0.001 | 0.164 |
| Non-PRCF residents: | | | | | | | | | | |
| >10, *n* (%) | 920 (61.0) | 287 (67.4) | 218 (71.5) | 91 (65.0) | 27 (75.0) | 0.019 | 0.001 | 0.397 | 0.125 | 0.679 |
| >20, *n* (%) | 377 (25.0) | 120 (28.2) | 112 (36.7) | 43 (30.7) | 17 (47.2) | 0.205 | <0.001 | 0.165 | 0.005 | 0.639 |

*p* value: Mann-Whitney *U* test for age (continuous), Pearson's Chi-square test *p* value (Yates corrected) for categorical variables; *>3 times a week; **percentage of patients among all HF subjects/among those with CKD. Abbreviations: IQR, interquartile range; CKD, chronic kidney disease (estimated glomerular filtration rate <60 mL/min/1.73 $m^2$); CAD, coronary artery disease; AMI, acute myocardial infarction; AF, atrial fibrillation; T2DM, type 2 diabetes mellitus; COPD, chronic obstructive pulmonary disease; PD, Parkinson's disease; CVA, cerebrovascular accident (stroke); TIA, transient ischaemic attack; Fracture types [Tr], trochanteric fractures; PRCF, permanent residential care facility; PTH, parathyroid hormone; OP, osteoporosis; LOS, length of stay.

In the total HF cohort mortality rates were slightly but significantly higher among males than females (6.6% vs. 4.8%, $p = 0.041$); although fatal events in the CKD group demonstrated also male prevalence, the difference did not achieve statistical significance (10.4% vs. 7.5%, $p = 0.095$).

Stratification by CKD stage revealed, as would be expected, the mortality rate increased dramatically with higher stages: 3.3%, 5.9%, 8.2%, 13.4%, 19.6% in stages 1 and 2, 3a, 3b, 4, 5, respectively (Table 2); the effect was most pronounced for CKD G4—G5 (OR 5.01, 95% CI 3.30–7.61, $p < 0.001$), CKD stage 5 accounted for the highest proportion of fatal outcomes in both females (22.7%) and males (16.7%) (Table 2). The mortality risk (adjusted for age and gender) was 1.50 (95% CI 1.00–2.24, $p = 0.049$), 2.06 (95% CI 1.35–3.15, $p = 0.001$), 3.47 (95% CI 2.16–5.57, $p < 0.001$) and 6.92 (95% CI 3.10–15.40, $p < 0.001$) fold higher for CKD stages 3a, 3b, 4, and 5, respectively, as compared to those with eGFR > 60 ml/min/1.73 $m^2$.

*3.3.2. Length of Hospital Stay (LOS).* Prolonged LOS (>10 days) occurred in 2053 (56.7%) HF patients, including 871 (60.3%) with CKD, of whom 416 (47.8%) had stage 3a, 288 (33.1%) had stage 3b, 132 (15.2%) had stage 4 and 35 (4.0%) had stage 5 (Tables 1 and 2). In the total HF cohort, a decrease in eGFR of 1 ml/min/1.73 $m^2$ increased risk of prolonged LOS (>10 days) by 1% (OR 1.01; 95% CI 1.00-1.01; $p < 0.001$). The CKD group displayed a considerably higher proportion of patients with prolonged hospital stay, and this was more noticeable among the non-PRCF residents (LOS >10 days: 68.7% vs. 61.0%, +7.7%, $p < 0.001$; LOS >20 days: 32.2% vs. 25.0%, +7.2%, $p < 0.001$) (Table 1). CKD increased the proportion of patients with LOS >10 days by 40% (OR 1.40; 1.18–1.67; $p = 0.001$), and the effect tended to correlate with the CKD stage: the OR (age and sex adjusted) for stage 3b was 1.35 (95% CI 1.02–1.78, $p = 0.036$), and the OR for stage 5 was 1.92 (95% CI 0.89–4.14, $p = 0.097$); the percentage of individuals with LOS>20 days was nearly 2-times higher among those in stage 5 compared to subjects in stage 3a (43.5% vs. 23.2%, $p = 0.005$) (Table 2).

To summarize, in HF patients, a greater eGFR loss was associated with higher risk for both a fatal outcome (more pronounced in males) and prolonged LOS.

*3.3.3. Antiosteoporotic Drug Usage and Outcomes.* Pre-fracture treatment with antiresorptive medications (bisphosphonate or denosumab) was associated with a slight trend to lower mortality rates in the total HF cohort (3.5% vs. 5.5%, $p = 0.079$), but in the CKD group the effect was statistically insignificant (7.2% vs. 8.3%, $p = 0.656$; the lowest usage of antiresorptive drugs was observed in the fatal non-CKD group (7.0% vs. 9.3%). Active antiosteoporosis therapy prior to the HF did not affect the LOS in patients with or without CKD.

*3.4. Prognostic Significance of Renal Status in Patients with Hip Fracture.* In the total HF cohort, the multivariate logistic regression after adjustment for relevant chronic conditions (all with $p < 0.150$ on univariate analyses), including history of T2DM, CAD, AMI, AF, anaemia, COPD, dementia, HF type, PTH and vitamin D status, PRCF residency, and controlling for age and gender, revealed the following seven characteristics as independent and significant risk factors for a lethal outcome: CKD (OR 1.86, 95% CI 1.35–2.57. $p < 0.001$), COPD (OR 1.70, 95% CI 1.18–2.45. $p = 0.004$), AF (OR 1.53, 95% CI 1.09–2.14. $p = 0.013$), 25 (OH) vitamin D ≤25 nmol/L (OR 1.68, 95% CI 1.18–2.38. $p = 0.004$), PTH >6.8 pmol/L (OR 1.39, 95% CI 1.01–1.92. $p = 0.041$), male sex (OR 1.46, 95%CI 1.04–2.05, $p < 0.027$), and age (OR 1.05, 95%CI 1.03–1.08. $p < 0.001$). When age as a continuous variable was substituted by age >80 years (OR 1.68, 95% CI 1.12–2.50. $p = 0.012$). The OR for CKD (G3-5) was 2.00 (95% CI 1.45–2.75, $p < 0.001$), for CKD G3 the OR was 1.70 (95% CI 1.20–2.39, $p = 0.003$) and for CKD G4-5 the OR was 3.15 (95% CI 1.96–5.08, $p < 0.001$), while all other risk factors remained practically unchanged.

Notably, the independent risk factors for a lethal outcome in HF patients with and without CKD demonstrated similarities and differences. CKD incorporates prognostic information of most chronic conditions which indicate a high risk of in-hospital mortality on univariate analysis such as CAD, anaemia, AF, COPD, dementia, hyperparathyroidism, vitamin D deficiency, PRCF residency, whereas in patients without CKD the independent prognostic indicators for hospital death include T2DM (OR 2.03, 95% CI 1.09–3.79, $p = 0.025$), AF (OR 1.77, 95% CI 1.03–3.04, $p = 0.040$), dementia (OR 1.77, 95% CI 0.99–3.15, $p = 0.054$), vitamin D deficiency (OR 1.97, 95% CI 1.13–3.45, $p = 0.017$), and elevated PTH levels (OR 1.68, 95% CI 1.03–2.73, $p = 0.038$).

CKD was also an independent predictor for prolonged hospital stay (>10 days) with an OR of 1.22 (95% CI 1.01–1.47, $p = 0.040$); other independent predictors of LOS >10 days were dementia (OR 1.73, 95% CI 1.32–2.28, $p < 0.001$), 25 (OH) vitamin D ≤25 nmol/L (OR 1.27, 95% CI 1.00–1.62. $p = 0.052$), and age (OR 1.03, 95% CI 1.01–1.04, $p < 0.001$; for aged >80 years OR 1.41, 95% CI 1.18–1.69, $p < 0.001$). The independent indicators of LOS >20 days were the same. Advanced age, dementia, and vitamin D deficiency independently predicted prolonged LOS in patients with and without CKD; in the latter group CAD (OR 1.49, 95% CI 1.09–2.03, $p = 0.013$) and AF (OR 1.38, 95% CI 1.01–1.89, $p = 0.045$) were also independent indicators of LOS >20 days.

Taken together, the presented data strongly suggest that in HF patients, CKD is an independent risk factor for both lethal outcome and prolonged hospital stay; the adverse effects parallel the severity of CKD and increase with age. Regarding the role of comorbid conditions in the development of an adverse outcome, patients with and without CKD demonstrated similarities and differences. In both groups advanced age and vitamin D deficiency were independent predictors of mortality as well as prolonged hospital stay. In contrast, only in non-CKD patients did the presence of T2DM, AF, COPD, dementia, and hyperparathyroidism independently predict hospital death, whereas CAD and AF predicted long hospital stay.

*3.5. Impact of Specific Characteristics on Outcomes in Hip Fracture Patients with CKD.* Both CKD and HF are strongly related with age, gender and many chronic diseases affecting morbidity and death. Understandably, multimorbidity may contribute to poor outcomes in HF, and CKD per se is not the only factor responsible for poor survival and longer LOS.

To determine the impact of specific diseases and conditions (which overlap, interact, or co-occur) on all-cause postoperative mortality and LOS in HF patients with CKD a Poisson regression analysis was performed (Table 3). The incidence rate ratio (IRR) for in-hospital death was 2.51 (crude), 2.06 (after adjustment for age as a continues variable and gender), and 1.67 (after further adjustment for 12 main comorbidities, HF type, mobility, lifestyle factors and laboratory characteristics which influenced fatal outcome on univariate analyses with $p \leq 0.150$). As shown in Table 3, in HF patients with CKD in comparison to the non-CKD group, the incidence of a lethal outcome (after multivariate adjustment for all the confounders listed in the footnotes to Table 3) was 106% higher among aged ≥80 years, 138% higher among walking aids users, 92% higher among PRCF residents and 88% higher in females. The risk of a lethal outcome increased significantly in CKD patients with hyperparathyroidism (+129%), hypertension (+106%), CAD (+79%), trochanteric fracture (+76%), and anaemia (+71%), it was nearly 8-fold higher in the small group of current smokers. On the other hand, in the fully adjusted Poisson models, no significant interaction with T2DM, previous MI, presence of AF, COPD, dementia, PD, CVA/TIA, vitamin D deficiency/insufficiency, higher alcohol consumption, history of smoking or administration of antiosteoporotic medications was observed, although in the unadjusted or adjusted only for age and gender models most of these characteristics demonstrated a significant influence on mortality indicating non-independent effects of these variables (Table 3). The significantly higher IRR for hospital mortality among patients who received anti-OP drugs (statistically significant only in the unadjusted model) reflects, likely, more frequent prescription of this treatment to individuals with more severe comorbid conditions, including OP.

Similar Poisson analyses with respect to LOS >10 days showed that presence of CKD increased the incidence of prolonged stay by 13% (unadjusted model) but this effect was not significant after adjustments. However, further analyses revealed that CKD associated with specific factors substantially and independently prolonged LOS. Namely, the IRRs for LOS >10 days among HF patients with CKD was significantly higher in subjects >80 years of age (+50%), with T2DM (+64%), anaemia (+45%), CAD (+38%), hypertension (+22%), or hyperparathyroidism (+36%), and lower in individuals with PD (−48%); other characteristics, including history of AMI, AF, dementia and male gender, affected significantly the IRR only in unadjusted or partially (for age and gender) adjusted models (Table 3).

To summarize, in HF patients with CKD, compared to the non-CKD group, the IRRs for both in-hospital mortality and prolonged LOS were independently and significantly affected by the age (>80 years), co-existing hypertension, CAD, anaemia, and elevated PTH. In individuals with CKD, the IRRs for a lethal outcome were also 1.8–7.8-times higher when one of the following conditions occur: trochanteric fracture, using a walking aid, being a PRCF resident, active smoker, whereas presence of T2DM increased the IRR for prolonged LOS.

*3.6. Performance of CKD Grade and Related Characteristics as Predictors of Outcome in Patients with Hip Fracture.* Based on the abovementioned findings on outcome prognostic indicators we further evaluated the discriminative ability (performance parameters) of CKD to predict, at admission, in-hospital mortality, and prolonged LOS, considering CKD grade, advanced age (>80 years), and presence of an additional specific comorbid condition (Table 4). In these analyses the CKD patients were divided into two subgroups: stage 3 (grades 3a and 3b were analysed together) and stages 4-5 (analysed together).

In all patients with CKD G3, the OR for mortality was 2.16, in the aged >80 years 4.19. In this group the OR increased dramatically if CKD was accompanied by dementia (OR 5.43), AF (OR 5.61), vitamin D deficiency (OR 5.70), anaemia (OR 6.98), CAD (OR 7.63), history of AMI (OR 8.51), hyperparathyroidism (OR 9.75), or COPD (OR 10.48).

The risk of a lethal outcome in all HF patients with CKD stages 4-5, compared to the non-CKD group, was 5-fold higher (OR 5.01) and 10-times higher among aged >80 years (OR 9.95); the highest OR demonstrated aged subjects with hyperparathyroidism (OR 20.97), vitamin D deficiency (OR 18.54), anaemia (OR 17.77), CAD (OR 17.14), COPD (OR 15.93), AF (OR 14.12), or history of AMI (OR 12.91), CVA/TIA (OR 12.67). The mortality risk in aged >80 years with CKD G4-5 and each of these conditions was 2-3 times higher than in CKD G3 patients (Table 4; Figure 1).

Notably, although mentioned factors demonstrated a high OR for hospital mortality, not all of them had a reasonable predictive performance. The ROC analyses (area under the receiver operator characteristic curve (AUC)) indicated that presence of CKD G3, even in patients aged >80 years, had a low-modest predictive value (AUC 0.593 for the total G3 group and 0.652 for the G3 aged >80); however, the predictive performance was reasonable in the group CKD G3 aged >80 years with COPD (AUC 0.744), CAD (AUC 0.733), hyperparathyroidism (AUC 0.715), anaemia (AUC 0.708), or dementia (AUC 0.700). Other clinical characteristics (including AF, T2DM, hypertension, PD, history of CVA/TIA, malignancy, vitamin D deficiency/insufficiency) did not significantly improve the prediction of postoperative mortality (the AUC was under 0.700).

The sensitivity, specificity, PPV, NPV, and other performance parameters of models based on different conditions associated with CKD G3 varied broadly (as expected with less sensitive variables being more specific). Sensitivity of 75% and above demonstrated only models which included hyperparathyroidism (89.4%), or anaemia (83.3%), or CAD (76.3%), or vitamin D insufficiency (75.7%). On the contrary, the specificity was above 75% in models with history of AMI (92.5%), COPD (86.3%), vitamin D deficiency (81.3%),

Table 3: Incidence rate ratios (IRRs) for all-cause in-hospital mortality and prolonged hospital stay (>10 days) in patients with hip fracture and chronic kidney disease (CKD): effects of socio-demographic factors and comorbidities (Poisson regression analyses).

| Variable | Model 1 | | Model 2 | | Model 3 | |
|---|---|---|---|---|---|---|
| | IRR (95% CI) | $p$ value | IRR (95% CI) | $p$ value | IRR (95% CI) | $p$ value |
| *In-hospital mortality* | | | | | | |
| No CKD | Ref. | — | Ref. | — | Ref. | — |
| CKD | 2.51 (1.87–3.37) | <0.001 | 2.06 (1.52–2.79) | <0.001 | 1.67 (1.19–2.32) | 0.003 |
| Age >80 years | 2.74 (1.97–3.81) | <0.001 | 2.76 (1.99–3.84) | <0.001 | 2.06 (1.44–2.96) | <0.001 |
| Female gender | 2.66 (1.86–3.81) | <0.001 | 2.15 (1.49–3.11) | <0.001 | 1.88 (1.26–2.80) | 0.002 |
| Male gender | 2.20 (1.31–3.70) | <0.001 | 1.88 (1.10–3.22) | 0.021 | 1.31 (0.73–2.36) | 0.359 |
| Fracture types (T) | 2.88 (1.89–4.39) | <0.001 | 2.26 (1.46–3.49) | <0.001 | 1.76 (1.10–2.82) | 0.018 |
| Anaemia | 2.97 (1.97–4.49) | <0.001 | 2.34 (1.53–3.58) | <0.001 | 1.71 (1.09–2.70) | 0.020 |
| Hypertension | 3.10 (2.07–4.65) | <0.001 | 2.55 (1.68–3.87) | <0.001 | 2.06 (1.31–3.23) | 0.002 |
| CAD | 2.82 (1.81–4.39) | <0.001 | 2.37 (1.50–3.74) | <0.001 | 1.79 (1.07–2.99) | 0.027 |
| History of AMI | 3.19 (1.44–7.04) | 0.004 | 2.90 (1.28–6.58) | 0.011 | 1.78 (0.73–4.35) | 0.202 |
| AF | 2.47 (1.45–4.20) | 0.001 | 2.04 (1.18–3.53) | 0.011 | 1.68 (0.91–3.11) | 0.096 |
| COPD | 2.10 (1.14–3.84) | 0.017 | 1.83 (0.98–3.42) | 0.059 | 1.71 (0.85–3.45) | 0.132 |
| Dementia | 2.01 (1.28–3.16) | 0.002 | 1.53 (0.96–2.43) | 0.074 | 1.36 (0.81–2.31) | 0.249 |
| CVA/TIA | 2.21 (1.15–4.27) | 0.018 | 1.80 (0.91–3.53) | 0.090 | 1.30 (0.62–2.75) | 0.485 |
| PRCF resident | 2.64 (1.71–4.08) | <0.001 | 2.06 (1.32–3.23) | 0.002 | 1.92 (1.17–3.14) | 0.009 |
| Smoker | 5.28 (1.10–25.42) | 0.038 | 7.38 (1.45–37.55) | 0.016 | 7.77 (7.52–8.04) | <0.001 |
| Ex-smoker | 2.35 (1.02–5.42) | 0.046 | 2.37 (0.99–5.65) | 0.052 | 1.85 (0.73–4.70) | 0.198 |
| Walking aid user | 3.48 (2.13–5.67) | <0.001 | 2.82 (1.70–4.67) | <0.001 | 2.38 (1.38–4.11) | 0.002 |
| PTH >6.8 pmol/L | 3.06 (2.08–4.49) | <0.001 | 2.65 (1.78–3.94) | <0.001 | 2.29 (1.52–3.43) | <0.001 |
| 25 (OH) vitamin D ≤25 nmol/L | 2.30 (1.29–4.11) | 0.005 | 1.88 (1.04–3.42) | 0.037 | 1.60 (0.83–3.09) | 0.161 |
| 25 (OH) vitamin D ≤50 nmol/L | 2.31 (1.51–3.51) | <0.001 | 1.92 (1.25–2.97) | 0.003 | 1.46 (0.91–2.35) | 0.116 |
| Use of anti-OP drugs | 3.32 (1.15–9.55) | 0.026 | 2.89 (0.97–8.60) | 0.057 | 1.95 (0.58–6.54) | 0.280 |
| *Length of stay >10 days* | | | | | | |
| No CKD | Ref. | — | Ref. | — | Ref. | — |
| CKD | 1.13 (1.02–1.25) | 0.022 | 1.08 (0.97–1.20) | 0.157 | 1.10 (0.98–1.23) | 0.095 |
| Age >80 years | 1.54 (1.36–1.75) | <0.001 | 1.54 (1.36–1.75) | <0.001 | 1.50 (1.31–1.72) | <0.001 |
| Male gender | 1.16 (0.96–1.41) | 0.127 | 1.27 (1.03–1.55) | 0.022 | 1.13 (0.91–1.41) | 0.283 |
| Anaemia | 1.58 (1.35–1.84) | <0.001 | 1.53 (1.30–1.79) | <0.001 | 1.45 (1.22–1.72) | <0.001 |
| Hypertension | 1.35 (1.18–1.54) | <0.001 | 1.27 (1.11–1.46) | 0.001 | 1.22 (1.05–1.41) | 0.008 |
| CAD | 1.69 (1.41–2.04) | <0.001 | 1.58 (1.31–1.92) | <0.001 | 1.38 (1.12–1.70) | 0.003 |
| History of AMI | 1.72 (1.21–2.44) | 0.002 | 1.71 (1.19–2.46) | 0.004 | 1.03 (0.65–1.63) | 0.908 |
| AF | 1.47 (1.18–1.84) | 0.001 | 1.29 (1.03–1.63) | 0.029 | 1.16 (0.90–1.48) | 0.254 |
| T2DM | 1.75 (1.33–2.29) | <0.001 | 2.06 (1.55–2.73) | <0.001 | 1.64 (1.20–2.23) | 0.002 |
| Dementia | 1.49 (1.16–1.91) | 0.002 | 1.20 (0.93–1.55) | 0.159 | 1.22 (0.93–1.60) | 0.154 |
| PD | 0.46 (0.26–0.80) | 0.006 | 0.50 (0.28–0.89) | 0.018 | 0.52 (0.28–0.96) | 0.036 |
| Smoker | 0.44 (0.26–0.73) | 0.001 | 0.56 (0.33–0.94) | 0.029 | 0.65 (0.36–1.16) | 0.146 |
| Walking aid user | 1.26 (1.06–1.50) | 0.008 | 1.10 (0.92–1.31) | 0.314 | 1.12 (0.93–1.35) | 0.248 |
| PTH > 6.8 pmol/L | 1.81 (1.57–2.10) | <0.001 | 1.71 (1.47–1.98) | <0.001 | 1.36 (1.16–1.60) | <0.001 |

Model 1, not adjusted; Model 2, adjusted for age and gender (adjusted for age only adjusted for gender only for sex and aged >80 respectively); Model 3, adjusted for age, gender, hypertension, anaemia, CAD, history of MI, prior CVA/TIA, AF, COPD, type 2 diabetes mellitus, dementia, Parkinson's disease, malignancy, fracture type, residency, lifestyle characteristics (smoking status, alcohol consumption), mobility, PTH and vitamin levels as well as anti-resorptive medication use. Only statistically significant associations at least in one model are shown. Abbreviations: CKD, chronic kidney disease (estimated glomerular filtration rate <60 mL/min/1.73 $m^2$); CAD, coronary artery disease; AMI, acute myocardial infarction; AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident (stroke); TIA, transient ischaemic attack; PRCF, permanent residential care facility; PTH, parathyroid hormone; Fracture types [T], trochanteric neck of femur fractures; OP, osteoporosis; T2DM, type 2 diabetes mellitus; PD, Parkinson's disease.

or AF (79.3%). Accordingly, the positive predictive values (PPV) of the tests were quite low (ranging from 7.2% to 11.6%) but the negative predictive values (NPV) were very good (98.2%–99.1%). The models showed appropriate calibration: Hosmer-Lemeshow goodness-of-fit test statistic ranged from 2.5 to 12.3 (with corresponding $p$ value ranging between 0.139 and 0.963).

The AUC for predicting a fatal outcome in all patients with CKD stages 4-5 was 0.626, and for the aged >80 years 0.748; in the latter group, the AUC reached 0.821–0.805–0.781 among subjects with elevated PTH, anaemia, or CAD, respectively. The models based on these characteristics showed reasonable sensitivity (82.1%, 76.7%, and 66.7%, respectively), high accuracy (82.0%, 84.1% and 88.8%, respectively), high NPV (98.0%–99.1%) and adequate calibration.

The number of patients with given condition needed to predict (NNP) a fatal outcome in HF patients based only on the presence of CKD G3 was 28.6, based on CKD G3 and age >80 years was 18.5; the NNP decreased greatly when one of the following conditions were added to the model: history of COPD (NNP = 9.6), MI (NNP = 9.6), CAD (NNP = 13.0), vitamin D deficiency (NNP = 13.3), elevated PTH (NNP = 14.5),

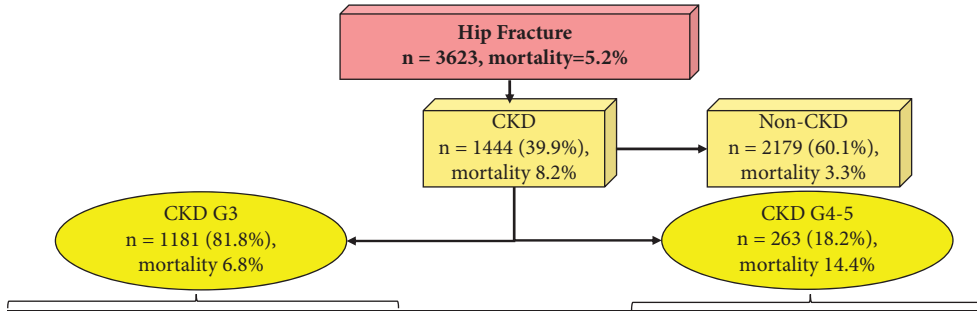
Table 4: Prognostic value and performance parameters of CKD severity, advanced age (>80 years) and comorbid conditions at admission to predict in-hospital mortality and prolonged length of stay (LOS >10 days) in patients with hip fracture.

| Comorbidity | OR (95% CI) | AUC (95% CI) | $p$ value | Sn (%) | Sp (%) | Acc (%) | PPV (%) | NPV (%) | LR (+) | LR (−) | NNP | HL, $p$ value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *In-hospital mortality* | | | | | | | | | | | | |
| CKD G3 ($n = 1181$) | 2.16 (1.55–3.00) | 0.593 (0.553–0.634) | <0.001 | 53.0 | 65.7 | 65.1 | 6.8 | 96.7 | 1.55 | 0.72 | 28.6 | 10.7, $p = 0.218$ |
| +Aged >80 years ($n = 957$) | 4.19 (2.41–7.28) | 0.652 (0.609–0.696) | <0.001 | 81.2 | 49.3 | 50.8 | 7.2 | 98.2 | 1.60 | 0.38 | 18.5 | 10.2, $p = 0.248$ |
| +COPD ($n = 129$) | 10.48 (4.48–24.51) | 0.744 (0.644–0.844) | <0.001 | 62.5 | 86.3 | 85.6 | 11.6 | 98.8 | 4.56 | 0.43 | 9.6 | 4.3, $p = 0.826$ |
| or +CAD ($n = 322$) | 7.63 (3.57–16.33) | 0.733 (0.663–0.803) | <0.001 | 76.3 | 70.3 | 70.5 | 9.0 | 98.7 | 2.57 | 0.34 | 13.0 | 2.5, $p = 0.963$ |
| or +PTH >6.8 pmol/L ($n = 541$) | 9.75 (3.83–24.83) | 0.715 (0.668–0.762) | <0.001 | 89.4 | 53.7 | 55.2 | 7.8 | 99.1 | 1.93 | 0.20 | 14.5 | 3.8, $p = 0.876$ |
| or +anaemia ($n = 461$) | 6.98 (3.07–15.88) | 0.708 (0.649–0.767) | <0.001 | 83.3 | 58.3 | 59.3 | 7.6 | 98.8 | 2.00 | 0.29 | 15.6 | 7.0, $p = 0.535$ |
| or +dementia ($n = 358$) | 5.43 (2.75–10.75) | 0.700 (0.629–0.770) | <0.001 | 71.4 | 68.5 | 68.6 | 8.4 | 98.3 | 2.27 | 0.42 | 14.9 | 6.3, $p = 0.612$ |
| or +AF ($n = 220$) | 5.61 (2.72–11.54) | 0.693 (0.606–0.781) | <0.001 | 59.4 | 79.3 | 78.7 | 8.6 | 98.3 | 2.87 | 0.51 | 14.5 | 12.3, $p = 0.139$ |
| or +vitamin D ≤25 nmol/L ($n = 183$) | 5.70 (2.71–11.95) | 0.690 (0.599–0.781) | <0.001 | 56.7 | 81.3 | 80.5 | 9.3 | 98.2 | 3.03 | 0.53 | 13.3 | 8.0, $p = 0.430$ |
| or +AMI ($n = 75$) | 8.51 (3.51–20.64) | 0.667 (0.561–0.772) | <0.001 | 40.9 | 92.5 | 91.2 | 12.0 | 98.4 | 5.45 | 0.64 | 9.6 | 5.8, $p = 0.666$ |
| or +vitamin D ≤50 nmol/L ($n = 427$) | 3.43 (1.60–7.36) | 0.641 (0.569–0.713) | 0.001 | 75.7 | 52.4 | 53.4 | 6.6 | 98.0 | 1.59 | 0.46 | 21.7 | 4.4, $p = 0.818$ |
| or +CVA/TIA ($n = 196$) | 3.03 (1.31–7.01) | 0.616 (0.512–0.720) | 0.014 | 43.5 | 79.7 | 78.9 | 5.1 | 98.3 | 2.14 | 0.71 | 29.4 | 13.8, $p = 0.086$ |
| or +T2DM ($n = 123$) | 2.92 (1.00–8.54) | 0.589 (0.471–0.707) | 0.094 | 31.2 | 86.5 | 85.5 | 4.1 | 98.6 | 2.31 | 0.80 | 37.0 | 5.3, $p = 0.729$ |
| CKD G4-5 ($n = 263$) | 5.01 (3.30–7.61) | 0.626 (0.581–0.671) | <0.001 | 34.9 | 90.4 | 87.9 | 14.4 | 96.7 | 3.64 | 0.72 | 9.0 | 7.1, $p = 0.528$ |
| +Aged >80 years ($n = 199$) | 9.95 (5.32–18.60) | 0.748 (0.679–0.818) | <0.001 | 66.0 | 83.7 | 82.9 | 15.6 | 98.2 | 4.05 | 0.41 | 7.2 | 8.3, $p = 0.407$ |
| +PTH >6.8 pmol/L ($n = 150$) | 20.97 (7.82–56.20) | 0.821 (0.747–0.894) | <0.001 | 82.1 | 82.0 | 82.0 | 15.3 | 99.1 | 4.56 | 0.22 | 6.9 | 6.7, $p = 0.566$ |
| or +anaemia ($n = 133$) | 17.77 (7.45–42.44) | 0.805 (0.727–0.883) | <0.001 | 76.7 | 84.4 | 84.1 | 17.3 | 98.8 | 4.92 | 0.28 | 6.2 | 9.2, $p = 0.325$ |
| or +CAD ($n = 99$) | 17.14 (7.46–39.41) | 0.781 (0.690–0.872) | <0.001 | 66.7 | 89.5 | 88.8 | 18.2 | 98.7 | 6.35 | 0.37 | 5.9 | 6.4, $p = 0.607$ |
| or +vitamin D ≤50 nmol/L ($n = 95$) | 10.66 (4.59–24.75) | 0.752 (0.657–0.846) | <0.001 | 65.4 | 84.9 | 84.0 | 17.9 | 98.0 | 4.33 | 0.41 | 6.3 | 6.6, $p = 0.581$ |
| or +hypertension ($n = 137$) | 7.40 (3.37–16.25) | 0.727 (0.639–0.814) | <0.001 | 66.7 | 78.7 | 78.1 | 14.6 | 97.7 | 3.13 | 0.42 | 8.1 | 2.8, $p = 0.949$ |
| or +AF ($n = 52$) | 14.12 (5.85–34.09) | 0.692 (0.588–0.795) | <0.001 | 43.5 | 94.8 | 93.4 | 19.2 | 98.3 | 8.37 | 0.60 | 5.7 | 11.7, $p = 0.163$ |
| or +vitamin D ≤25 nmol/L ($n = 36$) | 18.54 (7.29–47.13) | 0.687 (0.581–0.792) | <0.001 | 40.9 | 96.4 | 94.8 | 25.0 | 98.2 | 11.36 | 0.61 | 4.3 | 18.2, $p = 0.020$ |
| or +CVA/TIA ($n = 49$) | 12.67 (5.11–31.41) | 0.679 (0.573–0.784) | <0.001 | 40.9 | 94.8 | 93.3 | 18.4 | 98.3 | 7.87 | 0.62 | 6.0 | 16.2, $p = 0.040$ |
| or +dementia ($n = 67$) | 8.06 (3.17–20.49) | 0.662 (0.551–0.772) | <0.001 | 40.0 | 92.4 | 91.0 | 11.9 | 98.3 | 5.26 | 0.65 | 9.8 | 7.8, $p = 0.454$ |
| or +COPD ($n = 30$) | 15.93 (4.98–51.01) | 0.662 (0.531–0.792) | <0.001 | 35.7 | 96.6 | 95.5 | 16.7 | 98.8 | 10.50 | 0.67 | 6.5 | 7.5, $p = 0.486$ |
| or +T2DM ($n = 44$) | 8.82 (2.92–26.63) | 0.632 (0.514–0.749) | <0.001 | 31.2 | 95.1 | 93.8 | 11.4 | 98.6 | 6.37 | 0.72 | 10 | 18.3, $p = 0.019$ |

Table 4: Continued.

| Comorbidity | OR (95% CI) | AUC (95% CI) | $p$ value | Sn (%) | Sp (%) | Acc (%) | PPV (%) | NPV (%) | LR (+) | LR (−) | NNP | HL, $p$ value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Length of stay >10 days* | | | | | | | | | | | | |
| CKD G3 ($n = 731$) | 1.43 (1.19–1.73) | 0.539 (0.519–0.558) | <0.001 | 35.4 | 72.3 | 48.8 | 69.1 | 39.0 | 1.28 | 0.89 | 12.35 | 21.0, $p = 0.007$ |
| +Aged >80 years ($n = 554$) | 2.15 (1.69–2.73) | 0.591 (0.564–0.619) | <0.001 | 50.1 | 68.1 | 56.6 | 73.5 | 43.7 | 1.57 | 0.73 | 5.81 | 8.8, $p = 0.356$ |
| +Vitamin D ≤50 nmol/L ($n = 265$) | 2.55 (1.82–3.58) | 0.610 (0.572–0.648) | <0.001 | 50.7 | 71.3 | 58.9 | 72.8 | 48.8 | 1.77 | 0.69 | 4.63 | 11.0, $p = 0.203$ |
| or +hypertension ($n = 361$) | 2.22 (1.63–3.03) | 0.598 (0.561–0.635) | <0.001 | 57.2 | 62.4 | 59.1 | 72.3 | 46.0 | 1.52 | 0.69 | 5.46 | 9.5, $p = 0.301$ |
| or +PTH >6.8 pmol/L ($n = 324$) | 2.19 (1.62–2.97) | 0.592 (0.558–0.626) | <0.001 | 47.8 | 70.6 | 56.4 | 72.8 | 45.0 | 1.63 | 0.74 | 5.62 | 9.9, $p = 0.272$ |
| or +anaemia ($n = 261$) | 2.23 (1.62–3.07) | 0.587 (0.554–0.620) | <0.001 | 41.6 | 75.8 | 55.9 | 70.5 | 48.3 | 1.72 | 0.77 | 5.32 | 16.2, $p = 0.040$ |
| or +CAD ($n = 181$) | 2.51 (1.72–3.65) | 0.577 (0.548–0.606) | <0.001 | 30.0 | 85.4 | 52.4 | 75.1 | 45.4 | 2.05 | 0.82 | 4.88 | 8.7, $p = 0.367$ |
| or +dementia ($n = 102$) | 4.08 (2.37–7.01) | 0.567 (0.545–0.589) | <0.001 | 18.8 | 94.6 | 50.0 | 83.3 | 44.9 | 3.48 | 0.86 | 3.55 | 8.0, $p = 0.432$ |
| or +AF ($n = 131$) | 2.50 (1.63–3.81) | 0.559 (0.534–0.584) | <0.001 | 21.8 | 89.9 | 50.6 | 74.8 | 45.7 | 2.16 | 0.87 | 4.88 | 12.9, $p = 0.117$ |
| or +CVA/TIA ($n = 97$) | 2.08 (1.30–3.31) | 0.540 (0.516–0.563) | 0.003 | 16.7 | 91.2 | 49.1 | 71.1 | 45.7 | 1.90 | 0.91 | 5.95 | 25.3, $p = 0.001$ |
| or +osteoporosis ($n = 65$) | 2.91 (1.58–5.37) | 0.539 (0.519–0.559) | 0.001 | 12.6 | 95.3 | 47.6 | 78.5 | 44.4 | 2.68 | 0.92 | 4.37 | 18.5, $p = 0.018$ |
| or +COPD ($n = 68$) | 2.08 (1.20–3.63) | 0.532 (0.509–0.554) | 0.012 | 13.0 | 93.3 | 47.5 | 72.1 | 44.7 | 1.94 | 0.93 | 5.95 | 17.9, $p = 0.022$ |
| or +T2DM ($n = 64$) | 2.02 (1.15–3.57) | 0.528 (0.507–0.548) | 0.019 | 11.6 | 93.9 | 46.7 | 71.9 | 44.2 | 1.90 | 0.94 | 6.20 | 11.4, $p = 0.181$ |
| or +vitamin D ≤25 nmol/L ($n = 97$) | 1.84 (1.16–2.90) | 0.534 (0.509–0.559) | 0.012 | 16.6 | 90.2 | 48.4 | 69.1 | 45.1 | 1.69 | 0.92 | 7.04 | 12, $p = 0.152$ |
| CKD G4-5 ($n = 176$) | 1.30 (0.94–1.81) | 0.512 (0.497–0.527) | 0.137 | 11.4 | 91.0 | 42.0 | 67.0 | 39.0 | 1.27 | 0.97 | 16.67 | 24.0, $p = 0.002$ |
| +Aged >80 years ($n = 120$) | 1.12 (0.76–1.66) | 0.507 (0.483–0.531) | 0.630 | 14.9 | 86.5 | 45.9 | 59.2 | 43.7 | 1.10 | 0.98 | 34.48 | 24.3, $p = 0.002$ |
| +Vitamin D ≤50 nmol/L ($n = 57$) | 1.90 (1.06–3.43) | 0.536 (0.504–0.568) | 0.042 | 16.8 | 90.4 | 51.2 | 66.7 | 48.8 | 1.75 | 0.92 | 6.45 | 8.9, $p = 0.351$ |
| or +hypertension ($n = 81$) | 1.45 (0.88–2.38) | 0.527 (0.491–0.563) | 0.180 | 20.7 | 84.7 | 49.1 | 63.0 | 46.0 | 1.35 | 0.94 | 11.11 | 14.8, $p = 0.063$ |
| or +COPD ($n = 16$) | 3.50 (0.99–12.42) | 0.513 (0.501–0.525) | 0.071 | 3.8 | 98.9 | 45.6 | 81.2 | 44.7 | 3.45 | 0.97 | 3.86 | 11.4, $p = 0.181$ |
| or +AF ($n = 31$) | 0.61 (0.29–1.26) | 0.511 (0.495–0.527) | 0.243 | 96.4 | 5.8 | 54.5 | 54.3 | 58.1 | 1.02 | 0.62 | 8.06 | 26.7, $p = 0.001$ |
| or +CAD ($n = 61$) | 0.80 (0.47–1.36) | 0.509 (0.487–0.532) | 0.497 | 91.4 | 10.5 | 54.3 | 54.6 | 50.8 | 1.02 | 0.82 | 18.52 | 18.7, $p = 0.017$ |
| or +PTH >6.8 pmol/L ($n = 93$) | 1.08 (0.69–1.70) | 0.506 (0.475–0.536) | 0.813 | 17.0 | 84.1 | 47.0 | 57.0 | 45.0 | 1.07 | 0.99 | 50.00 | 12.6, $p = 0.127$ |
| or +anaemia ($n = 78$) | 1.09 (0.68–1.76) | 0.505 (0.477–0.533) | 0.818 | 14.0 | 87.0 | 49.0 | 53.8 | 48.3 | 1.08 | 0.99 | 47.62 | 17.9, $p = 0.022$ |
| or +dementia ($n = 25$) | 1.22 (0.54–2.76) | 0.503 (0.490–0.517) | 0.625 | 3.9 | 96.8 | 45.5 | 60.0 | 44.9 | 1.22 | 0.99 | 20.41 | 13.7, $p = 0.091$ |
| or +vitamin D ≤25 nmol/L ($n = 20$) | 1.23 (0.50–3.06) | 0.503 (0.490–0.517) | 0.823 | 3.4 | 97.2 | 45.6 | 60.0 | 45.1 | 1.21 | 0.99 | 19.61 | 11.4, $p = 0.182$ |
| or +CVA/TIA ($n = 23$) | 1.10 (0.47–2.53) | 0.502 (0.487–0.516) | 1.000 | 3.7 | 96.7 | 46.1 | 56.5 | 45.7 | 1.21 | 1.00 | 45.45 | 6.4, $p = 0.602$ |
| or +T2DM ($n = 26$) | 1.08 (0.49–2.39) | 0.501 (0.486–0.517) | 1.000 | 4.1 | 96.2 | 44.7 | 57.7 | 44.2 | 1.08 | 1.00 | 52.63 | 6.8, $p = 0.561$ |

[(1)]McFadden pseudo-R-squared; [(2)]Hosmer-Lemeshow goodness of fit test; [(3)]Sn, sensitivity; Sp, specificity; NPV, negative predictive value; PPV, positive predictive value; (−) LR, negative likelihood ratio; (+) LR, positive likelihood ratio; Acc, accuracy; NNP, number needed to predict.




| OR | AUC | NNP | | OR | AUC | NNP |
|---|---|---|---|---|---|---|
| 2.16 | 0.593 | 28.6 | CKD (all) | 5.01 | 0.626 | 9.0 |
| 4.19 | 0.652 | 18.5 | + Age > 80 years | 9.95 | 0.748 | 7.2 |
| 9.75 | 0.715 | 14.5 | +PTH>6.8 pmol/L | 20.97 | 0.821 | 6.9 |
| 7.63 | 0.733 | 13.0 | *or* + CAD | 17.14 | 0.781 | 5.9 |
| 6.98 | 0.708 | 15.6 | *or* + Anaemia | 17.77 | 0.805 | 6.2 |
| 5.70 | 0.690 | 13.3 | *or* +Vitamin D≤25 nmol/L | 18.54 | 0.687 | 4.3 |
| 5.61 | 0.693 | 14.5 | *or* + AF | 14.12 | 0.692 | 5.7 |
| 5.43 | 0.700 | 14.9 | *or* + Dementia | 8.06 | 0.662 | 9.8 |
| 10.48 | 0.744 | 9.6 | *or* + COPD | 15.93 | 0.662 | 6.5 |

Figure 1: Prognostic value and performance of CKD stage, advance age (>80 years), and comorbidities for predicting in-hospital mortality in patients with hip fracture. Abbreviations: OR, odds ratio; AUC, area under curve (receiver operating characteristic); NNP, number needed to predict; CKD, chronic kidney disease (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 $m^2$); CKD G3, chronic kidney disease stage 3 (eGFR 30–59 mL/min/1.73 $m^2$); CKD G4-5, chronic kidney disease stage 4 and 5 (eGFR <30 mL/min/1.73 $m^2$); PTH, parathyroid hormone; CAD, coronary artery disease; AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease.

AF (NNP = 14.5), dementia (NNP = 14.9), or anaemia (NNP = 15.6).

In patients with CKD G 4-5, the NNP in-hospital mortality was significantly lower: 9.0 for the total group, 7.2 for the aged >80 years, and decreased further in cases with hypertension (3.1), vitamin D insufficiency (4.3), AF (5.7), CAD (5.9), CVA/TIA (6.0), anaemia (6.2), COPD (6.5), or hyperparathyroidism (6.9) (Table 4, Figure 1).

In aged CKD G3 patients, compared to the non-CKD group, presence of one of following 7 comorbidities—CAD, anaemia, COPD, AF and dementia, hyperparathyroidism, or vitamin D deficiency—increased the risk of a fatal outcome by 10.5–5.5-times and demonstrated a reasonable predictive value (AUC ranged between 0.744 and 0.693) with an NNP of 9.6–15.6. The same factors in subjects with CKD G4-5 indicated a 21.0–8.1-times higher mortality risk, with predictive power up to 82.1% (AUC ranged between 0.821 and 0.662) and NNP of 3.1–9.8 (Table 4, Figure 1).

Among the 118 HF patients with CKD and a lethal outcome, at least one of three strongest predictive comorbidities (CAD, anaemia, elevated PTH) was observed in 106 (89.8%) subjects (in 87.5% with CKD G3 and in 94.7% with CKD G4-5), and one of 7 predictive comorbidities (CAD, anaemia, AF, dementia, COPD, elevated PTH or vitamin D deficiency) in 114 (96.6%) patients (96.2% and 97.4%, respectively).

In HF patients, presence of CKD G3 increased the risk of LOS >10 days by 43%, in subjects aged >80 years by 115%; the highest risk for prolonged LOS demonstrated individuals with dementia (OR 4.08), CAD (OR 2.51), AF (OR 2.50), anaemia (OR 2.23), vitamin D deficiency/insufficiency (OR 2.55), or elevated PTH (OR 2.19). However, none of the models based on these specific conditions achieved a valuable predictive level (the AUC ranged between 0.610 and 0.559). In CKD G4-5 subgroup aged >80 years, vitamin D deficiency/insufficiency nearly doubled risk of LOS >10 days (OR 1.90), while other studied factors did not demonstrate additional significant influence on LOS, although each was present in 87.5%–94.0% of these patients (Table 4). At least one of the 7 strongest indicators of poor outcome was found in 95.1% of patients with LOS >10 days (in 94.2% with G3 and in 98.8% with G4-5).

## 4. Discussion

*4.1. Main Findings.* (1) About 40% of elderly patients with an osteoporotic HF had CKD (9-times higher prevalence than in the total Australian population of the same age); (2) CKD

was independently associated with poor in-hospital outcomes with a 2.5-times (8.2% vs. 3.3%) higher mortality rate and a significantly higher number of patients with prolonged LOS; (3) in the CKD group, HF patients aged >80 years accounted for 85% of all in-hospital deaths, presence of comorbidities associated with CKD, especially CAD, anaemia, AF, dementia, COPD, elevated PTH and/or vitamin D deficiency, and substantially increased the risk of hospital death (by 2–3.5-fold) and prolonged LOS (by 22%–64%); (4) models based on three admission characteristics—CKD, age >80 years and one of abovementioned comorbid conditions—showed reasonable discriminative performance for predicting in-hospital death; (5) pre-HF CKD was rarely diagnosed and treated for OP.

*4.2. Prevalence of CKD among HF Patients and the General Population.* The reported prevalence of CKD throughout the world varied widely. The prevalence of CKD in the Australian general population of 3.6% [38–40]–4.6% [48] matches the previously reported incidence of 3.8% in Spain [49] but is lower than the globally estimated CKD (stages 3–5) prevalence of 6.3–10.2% [1, 5, 11, 50, 51]). In our HF cohort, CKD was diagnosed in 39.9% of all patients indicating that subjects with HF were about 3-9 times (based on global or Australian data, respectively) more likely to have kidney failure.

*4.3. CKD and HF.* It appears that CKD as a risk factor for HF remains largely underestimated. The association of CKD and fractures [22, 23, 49–55], including HF [24, 25, 51, 52, 55–62], was reported in many studies; patients with CKD have a two-to 100-fold higher incidence of fracture compared with age- and sex-matched individuals without CKD [22]. However, in some reports the inverse association between eGFR and fracture rates has not been observed [13, 63, 64]. Differences in the study designs (methods used to identify fractures and CKD, type and number of comorbidities, risk factors and confounding factors analysed, etc.) may at least partially explain the controversial results.

*4.4. CKD and Hospital Outcomes.* Relatively few studies have evaluated the eGFR and the risk of adverse outcomes in HF patients. In line with previous studies [29, 65], in our HF cohort CKD was associated with a higher number of comorbidities (in addition to CKD): three or more chronic conditions had 79.4% of those with CKD vs. 62.0% of those without CKD; the prevalence of comorbid conditions increased in parallel with CKD progression (from stage G3 to G5), which, in turn, dramatically magnified adverse outcomes.

CKD was associated with 62.4% of all in-hospital HF deaths and accounted for 42.4% of all cases with prolonged LOS (>10 days). Compared to non-CKD patients, the mortality rate in those with CKD G3 was 2-times higher (6.8%). in subjects with CKD G 4-5—4.4-times higher (14.4%), and for patients with an eGFR < 30 ml/min/1.73 $m^2$ -6-fold higher (19.6%); the effect on LOS also tended to correlate with higher CKD stage.

The observation that more severe CKD stage was associated with a higher risk of mortality is in line with most published reports [13, 26, 28, 60, 61, 65–74] on 30-day and 1-year mortality; a significantly higher LOS in HF patients with CKD was also reported [75]. Some authors, however, observed an increase of all-cause mortality only in patients with CKD stage G4 (but not with stages G3a, G3b, G5, G3–G5) [76] or stage G5 [75, 77], in one study of HF patients (>65-years of age) no significant association was observed between higher stages of impaired renal function and mortality [29], and in another study severity of CKD did not affect 1-year mortality rate and medical complications in patients with intertrochanteric fracture [77].

At the individual level, HF outcome is, understandably, dependant on the integrative effect of multiple factors (genetic, environmental, lifestyle, age, gender, comorbidities, medication used, perioperative complications), and the causal relationships include many interacting feedback loops. Kidney function is intimately interconnected with the performance of musculoskeletal, cardiovascular, endocrine, nervous, digestive, respiratory and immune systems; the communication between these organ systems that occurs through a myriad of bidirectional pathways (including the effects of calcium, phosphorus, magnesium, PTH, vitamin D, vitamin K, Klotho, a variety of osteokines [osteoprotegerin, osteocalcin, sclerostin, fibroblast growth factor 23, lipocalin-2, osteopontin; insulin-like growth factor-1, transforming growth factor], myokines [myostatin, irisin, follistatin, osteonectin, myonectin, FGF-21], proinflammatory cytokines [interleukins IL-6, IL-1, tumour necrosis factor alfa [TNF-$\alpha$], etc.], adipokines [leptin, adiponectin, resistin, ghrelin family peptides]) maintains optimal functioning (homeostasis/homeorhesis) of the human body. In disease states, abnormalities in any of these systems can initiate and perpetuate structural and functional dysfunction in other organs. Not surprisingly, renal impairment, abnormalities in mineral-bone metabolism, numerous diseases encompassing T2DM, CAD, hypertension, heart failure, anaemia, dementia, COPD, etc., activate each other (via the autocrine, paracrine and nervous systems), creating metabolic dysregulation and vicious cycles of damage [11, 27, 78, 79], leading to multimorbidity (i.e., renal osteodystrophy [80], cardiorenal syndrome [81], brain-kidney axis/cross-talk [82–87]; CKD—COPD interaction [78, 88]) which is strongly associated with falls and fractures (Figure 2). Clearly, in the elderly multiple chronic diseases, falls and fractures are competing events that cluster, and CKD is a risk factor for abovementioned conditions, death, and other adverse outcomes.

Therefore, we attempted to further delineate the relationship between CKD and the risk of adverse events with regard to sociodemographic and comorbid conditions at admission. Although the impact on mortality of CKD associated with different comorbidities including T2DM [89], CAD [5, 90–93], hypertension [94–96], COPD [97, 98], has been well described, the combined effect of CKD and specific comorbidities on HF outcome has not been systematically evaluated. We demonstrated that some coexisting factors (e.g., age, chronic conditions), as one might expect, may

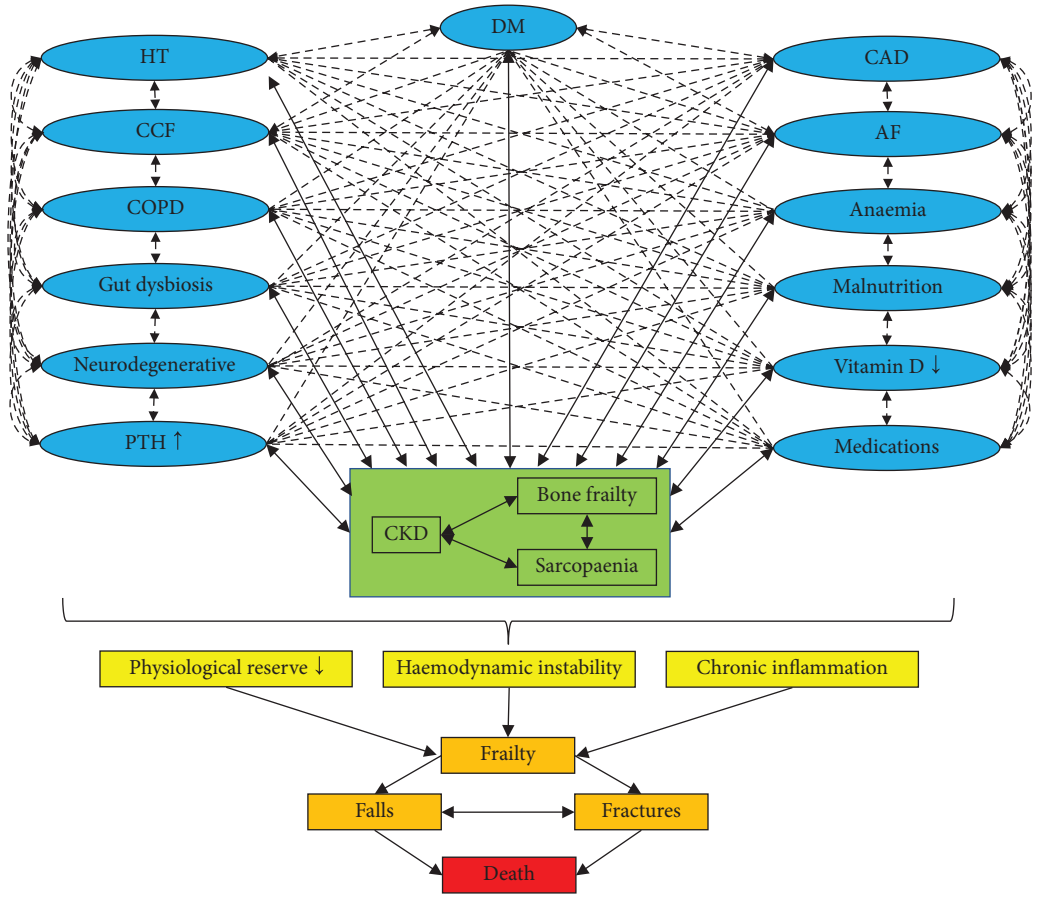



Figure 2: A simplified schematic illustrating the multidirectional interactions (direct and indirect) between CKD, musculoskeletal and other chronic systemic organ diseases contributing to falls, frailty, osteosarcopaenia, fractures, and poor outcomes. The centre of the figure depicts the bi-/multidirectional CKD-bone axis, CKD-skeletal muscle axis, and bone-muscle axis as pivotal determinants of musculoskeletal health; the components of the homeostatic kidney—bone-skeletal muscle axes are linked with and integrated in the structure and function of all other organ systems (cardiovascular, endocrine, nervous, immune, digestive, hematopoietic, respiratory, and adipose tissue), each of which, in turn, interacts one with another. A myriad of molecular mechanisms are involved in these network and feedback loops within and outside the CKD-musculoskeletal axes; the most extensively investigated include calcium, phosphorus, magnesium, PTH, vitamin D, vitamin K, Klotho, osteokines (osteoprotegerin; osteocalcin, sclerostin, fibroblast growth factor 23, lipocalin-2, osteopontin; insulin-like growth factor-1, transforming growth factor), myokines (myostatin, irisin, follistatin, osteonectin, myonectin, FGF-21), proinflammatory cytokines (interleukins IL-6, IL-1, tumour necrosis factor alfa [TNF-$\alpha$], etc.), and a variety of adipokines (leptin, adiponectin, resistin, ghrelin family peptides, etc.). The pathophysiology of osteosarcopaenia and poor outcome in CKD includes genetic susceptibility, and is linked with age, environmental, lifestyle (physical activity, malnutrition, smoking, alcohol overuse, etc.), and disease related (CKD and associated disorders) changes, as well as the effects of numerous medications (drugs used to treat each of abovementioned conditions can have effects that impact the musculoskeletal and other organ system, and vice versa). All these factors interact and participate in the regulation networks integrating the multi-organ interactions in health and disease. Hip fracture patients with CKD have more comorbidities, more severe clinical complications, and a significantly higher risk of poor outcome (in-hospital death, prolonged length of stay) compared with individuals without CKD. The tight relationships between the CKD—musculoskeletal axes and diseases of other organ systems (shown in blue ovals) are indicated by thick solid bidirectional arrows, the interconnections between the different organ system disorders are shown by thin dashed lines. Abbreviations: AF, atrial fibrillation; CCF; CKD, chronic kidney disease; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HI, haemodynamic instability; HT, hypertension; PTH, parathyroid hormone.

have a profound aggravating effect on hospital mortality and LOS, but not all comorbidities are the same with regards to their impact on poorer outcome; the magnitude of their effects were different. In HF patients with CKD, compared to the non-CKD group, the IRRs for both in-hospital death and prolonged LOS were independently and significantly affected by the age (>80 years), co-existing hypertension, CAD, anaemia, and elevated PTH. In individuals with CKD, the IRRs for a lethal outcome were also 1.8–7.8-times higher when one of the following signs occurred (combined effect): trochanteric fracture, walking aid use, being a PRCF resident or being an active smoker, whereas presence of T2DM increased the IRR for prolonged LOS. Our findings are in accordance with the literature showing a significantly higher mortality rate in HF patients with CKD of advanced age [26, 27, 29, 70, 75, 99]. Male gender was also reported as a significant risk factor for a fatal outcome [26, 29, 99], although females who represent nearly 3/4 among HF

patients are more susceptible to CKD [5, 11]. Our data, in agreement with many reports [100–103], showed that male gender was an independent predictor of hospital death when the total HF cohort was analysed; gender, however, did not independently affect the outcome in HF patients with CKD, despite male prevalence among the CKD G5 group (52.2%). CKD progression is thought to be faster in men [104], possibly due to sex-related differences in biological, lifestyle and socioeconomic factors [105]. Contrary to some reports that the anatomic type of HF does not affect mortality [29], we found (in multivariate regression analysis) that the risk of hospital death is 76% higher in patients with trochanteric compared to a cervical fracture (Table 3).

A number of studies (but not all [106]) concluded that use of antiresorptive medications improved survival [30, 107–116]. Our study does not have sufficient statistical power to reach the same conclusions. In our HF cohort, the vast majority of patients were not investigated or treated for OP, antiresorptive medications were rarely used in the months preceding the fracture, with no difference between patients with and without CKD. In many countries a wide therapeutic gap in OP/OF management (underdiagnosis and undertreatment) in the general population as well as in patients with CKD has been reported [36, 117–124].

*4.5. Prognostic Value of CKD and Related Factors for Predicting In-Hospital Outcome.* We estimated separately the prognostic value of CKD G3 and CKD G4-5 in association with advanced age (>80 years) and each of 12 different chronic comorbid conditions to predict in-hospital all-cause mortality and LOS (Table 4 and Figure 1). To our knowledge, this is the first study investigating the topic of HF outcome prediction in such a way. We showed that in HF patients aged >80 years (individuals most vulnerable or at risk of in-hospital death and/or prolonged LOS), the presence of CKD and at least one common chronic comorbidity acted as a suitable indicator of poorer outcomes; the predicting performance of models based on any comorbidity (CAD, anaemia, dementia, AF, COPD, hyperparathyroidism, or vitamin D deficiency) was of acceptable validity. The models based only on three variables (CKD stage, age, and a comorbid condition) were able to predict fatal outcomes with good discrimination capability (AUC $\geq$ 0.700) and accuracy (70.5%–95.5%). Notably, patients with the same CKD stage but different comorbidities were not at equal risk for an adverse outcome.

The impressive data was that HF patients aged >80 years with CKD G3 had a 5.4–10.5-fold higher risk of a fatal outcome if hyperparathyroidism, vitamin D insufficiency, CAD, anaemia, AF, COPD, or dementia coexisted, whereas in subjects with CKD G4-5 and one of the mentioned comorbidities the risk was 8.1–21.0-fold higher compared to patients without these characteristics (Figure 1). Moreover, the number of patients needed to be examined for correct prediction decreased among CKD G3 patients from 28.6 (based only on CKD stage) to 9.6–14.5 when only age and one of the comorbidities were taken into account, and for patients with CKD G4-5 from 9.0 to 4.3–7.2, respectively.

An example supporting the clinical relevance of this novel approach, as shown in Table 4 and illustrated in Figure 1 follows: Compared to a HF patient without renal impairment, the risk of a lethal outcome in a HF person >80 years old with GFR of 59–45 ml/min/1.73 $m^2$ (CKD G3a) is 4.2-times higher (AUC 0.652) and with GFR <45 ml/min/1.73 $m^2$ is 9.9-times higher (AUC 0.748); if CKD is associated with CAD the risk is 7.6 (AUC 0.733) and 17.1 (AUC 0.781)-times higher, respectively; and if hyperparathyroidism is present the risk is 9.8 (AUC 0.715)- and 20.97 (AUC 0.821) higher, respectively; and if the subject is diagnosed with COPD the risk is 10.5 (AUC 0.744)- and 15.9 (AUC 0.662)-times higher.

Our results and the literature indicate that increased mortality after HF surgery is not caused by the fracture itself but rather reflects reduced physiologic capacities pre-HF and deteriorating health status due to different chronic diseases, among which CKD and related comorbid conditions play a leading role. Notably, fatal outcomes are the result of multiple influences, and the causal relationships include many interacting feedback loops affected pre-, intra-, and post-operatively.

*4.6. Practical Considerations.* Our results are of considerable practical importance regarding HF management in the perioperative period and may help to optimise current OF/OP prevention strategies in general.

The usefulness of preoperative assessment and optimisation of renal function and CKD-related conditions in HF patients is at least threefold: (1) proper risk stratification, decision-making and prediction of post-fracture surveillance, (2) prevention of potentially dangerous perioperative interventions (i.e. use of nephrotoxic iodinated radiocontrast) and medications (aminoglycosides, cyclosporin A, cisplatin, amphotericin B, nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin converting enzyme (ACE)-inhibitors, angiotensin receptor blockers, diuretics etc.), as well as drugs which may negatively affect bone and muscle metabolism, cause haemodynamic instability and predispose to falls, and (3) early identification and monitoring patients at-risk to prevent short- and long-term complications by individualising therapy, focussing on modifiable risk factors (i.e., anaemia, hypertension, arrhythmias, electrolyte disturbance, vitamin D deficiency, hyperparathyroidism, smoking, malnutrition, emotional distress, high-dose narcotic use, etc.), reducing the effects of specific comorbid diseases (i.e., T2DM, CAD, AF, COPD) and timely introduction of appropriate preventative and therapeutic treatments. The outcomes, particularly survival, after HF surgery seemed to be affected more by chronic comorbidities than by other factors. The predictive models presented here are simple to apply at admission and may help identify patients in whom relevant preventative measures can reduce adverse outcomes.

Our results provide also additional data supporting the need of a conceptual change in the view of OP/OF as a musculoskeletal disease to that of a systemic disorder emphasising the significance for holistic strategies for

evaluation, prediction, prevention, and long-term management of individuals at risk of both CKD and OP/OF.

Worldwide, the absolute number of patients with CKD as well as with OP/OFs, including HF, is increasing, especially with advancing age, and the high burden of morbidity and mortality over the past decades remains unchanged or is increasing [125, 126]. Both CKD and OP/OFs are heterogenic (e.g. in T2DM the heterogeneous spectrum of CKD and associated osteosarcopaenia includes diabetic and various non-diabetic kidney disease [127–129]), share common risk factors and complex multifactorial pathophysiological mechanisms, and are multi-directionally interlinked (with progress of one usually causing deterioration of the other). Both diseases are usually clinically silent, slowly progressive, often associated with multimorbidity, prevalent in women and the elderly, and have a strong impact on morbidity, mortality, and public health costs. Musculoskeletal and renal structure and function usually decline in parallel with ageing [11, 15, 23] and the incidence of fractures increases with deterioration of kidney function. However, both diseases are still underdiagnosed or diagnosed at advanced/irreversible stages and are undertreated [6, 8, 23, 76, 130].

Concerning medical therapy, both CKD and OP/OF are associated with polypharmacy [131–137]. The situation is further complicated by the fact that the kidney, the main organ that eliminates xenobiotics, is vulnerable and predisposed to the toxic effects of drugs and their metabolites. The literature on the effects of different drugs on the renal and musculoskeletal systems is contradictory. The medications used may have opposing effects on kidney function, musculoskeletal status, CKD-related diseases, and falls (especially in the management of "discordant and unrelated conditions"-[131, 138]).

Multiple (but not all) studies and meta-analyses found that usage of antipsychotics (typical and atypical), antidepressants (tricyclic and serotonin reuptake inhibitors), antiparkinsonian drugs or anticonvulsants was associated with a negative effect on BMD, higher falls and fracture risk including HF [139–142], as well as increased risk of acute kidney injury, CKD, hypertension, cardiovascular events, etc. [143–146]. NSAIDs may increase risk of acute kidney injury and/or worsening hypertension [138], the glucocorticoid induced OP/OF is common [147]. An increased fall and fracture risk was observed in users of glucocorticoids, benzodiazepines, vasodilators, antihypertensive drugs (alpha- and beta-adrenergic receptor blockers, calcium channel blockers, angiotensin converting enzyme [ACE] inhibitors, angiotensin II receptor blockers), loop diuretics (in contrast to thiazide diuretics [148], proton pump inhibitors and coumarin anticoagulants [139, 140, 149–151], however, according to a recent systematic review, deprescribing drugs that increased fall-risk did not change the rate of falls [152]. Treatment of dyslipidaemia, the mainstay of CVD prevention (and decreasing the main cause of mortality), also may contribute to bone and muscle health. Data on association between lipid status and the effects of hypolipidemic therapy on bone metabolism is mixed. Both a negative relationship between total cholesterol and low-density lipoprotein cholesterol concentrations and BMD [153–158] and a positive association between high-density lipoprotein cholesterol and BMD [159] have been reported. Other studies, however, found that higher serum high-density lipoprotein cholesterol and apolipoprotein B levels (traditionally viewed as a protective for CVD factor) reduced BMD and may increase the risk of osteoporotic fracture (including HF) independently of traditional risk factors for fractures [160–166]. This may possibly occur by reduction of osteoblast numbers [167] or function via rare adverse genetic variants [168]. In general, statins may slightly increase BMD and reduce fracture risk [154, 169]. The effects of ezetimibe, fibrates, and niacin remain unknown, whereas bone resorption inhibitors (nitrogen-containing bisphosphonates and selective estrogen receptor modulators) reduce serum cholesterol levels [170].

Management of "concordant" conditions is also complex. For example, in T2DM, the most common cause of CKD and a significant risk factor for OFs, the association between fracture risk and the use of different antidiabetic drugs (even of the same class with similar pharmacological mechanism) varied significantly [171]. Some dipeptidyl peptidase-4 inhibitors (linagliptin, alogliptin) reduced fracture risk, while others (omarigliptin, sitagliptin, vildagliptin, saxagliptin, and trelagliptin) demonstrated an opposite effect; glucagon-like peptide-1 receptor agonists (albiglutide, dulaglutide, exenatide, liraglutide, semaglutide, and lixisenatide), sulfonylureas (glipizide, gliclazide, glibenclamide, and glimepiride), metformin, insulin and alpha-glucosidase inhibitors (voglibose) possibly decrease the risk of fracture and protect against sarcopaenia [171, 172], while use of thiazolidinediones (rosiglitazone, pioglitazone) may elevate fracture risk, but protect against dementia [173], markedly in persons with T2DM, who have a history of CAD or stroke [174].

During the last decade, sodium-glucose cotransporter inhibitors (SGLT2i), drugs initially developed as insulin independent hypoglycaemic agents, demonstrated useful cardio- and reno-protective properties and became the therapeutic cornerstone in patients having T2DM, especially complicated with CKD and heart failure [175–177]; SGLT2i have also been enthusiastically introduced for widespread utilisation as a standard-of-care treatment for patients without T2DM [178]. Some studies concluded that canagliflozin and dapagliflozin decreased the risk of fracture, whereas empagliflozin and ertugliflozin may increase the fracture risk [171]. The mechanism of the latter outcome, which increased over time medication used, was explained by negative effects on bone metabolism (rises of both serum phosphate and PTH levels, decreases in 1,25-dihydroxyvitamin D levels) [176, 179–181]. Other studies, however, did not confirm a SGLT2i-fracture association [182, 183]; the question whether these agents should be prescribed or withheld in individuals at high risk for OP/OFs requires careful consideration of the risk/benefit balance. The complexity and uncertainties regarding pharmacotherapy underscore the need for appropriate individualisation and highlights the importance for further investigation. Meanwhile, the abovementioned controversies and examples offer

a glimpse into the decision-making that might be used to personalize (by balancing the benefits and harms of the therapy) and more effectively target treatment of CKD/OP/OF.

The high prevalence of CKD among HF patients, its negative effects on outcomes, the close (patho-) physiological coupling between kidney and the musculoskeletal system in health and disease (the bi/multidirectional influences), associations with a number of comorbid conditions which negatively affect musculoskeletal metabolism and mass, predisposing to osteosarcopaenia, falls and fractures–all these factors strongly indicate the importance to accurately identify and treat people with renal impairment early as subjects at high risk of OP/OF and *vice versa*. Even early stages of renal dysfunction should be recognised and interpreted as risk predictors of future OFs.

Importantly, kidney function may be significantly impaired before OP or other related CKD-related comorbidities are diagnosed or OF occurred. For example, in a national cohort of 36,764 US veterans CKD was evident in 31.6% of veterans prior to being diagnosed with T2DM [184].

Most (if not all) of current OP/OF management strategies (screening and prevention) focus only on bone status; therapeutic interventions directly target the balance between bone production and bone resorption and rarely include even falls prevention. Little attention is given to the possibility of modulating bone and muscle health through early detection and appropriate progression-delaying treatment of extra-skeletal diseases, especially impaired renal function (CKD), which in combination with associated disorders in other organ system affects musculoskeletal health, predisposes to falls and, consequently, fractures. However, recent clinical guidelines are not consistent in their incorporation of CKD measures for OP/OF risk prediction, CKD is not mentioned in the list of secondary causes of osteoporosis [23], and in patients with CKD stage3a-5 BMD testing is recommended only when there is evidence of, or risk factors for, OP and if "a low or declining BMD will lead to additional interventions to reduce falls or use osteoporosis medications" [55, 185].

Moreover, although early identification of patients who may have underlying risk for CKD/OP/OF is paramount for effective interventions aimed to slow the disease's progression, current fracture risk assessment tools (The Fracture Risk Assessment Tool [FRAX]; Garvan Fracture Risk Calculator) do not account for CKD [23, 186–188] or falls [36]. On the other hand, it has been shown that FRAX predicts (modestly) major osteoporotic fractures and HFs risk in patients with non-dialysis CKD [189–192], in haemodialysis patients [193, 194] and kidney transplant recipients [195, 196] but performs no better than BMD alone [190].

It is time to integrate CKD in management of OP/OF: a high index of suspicion for OP/OF is essential when treating individuals with renal dysfunction and CKD-related diseases. Screening for bone-mineral status, reviewing for specific comorbidities (in particular, CAD, AF, T2DM, anaemia, COPD, dementia, frailty) and medications used (e.g., glucocorticoids, psychotropics, antidiabetics, etc.) should be performed routinely in all adults. On an individual and population levels risk factors for OP/OF in CKD could be modified by lifestyle and dietary changes and reducing to a minimum drugs affecting bone/muscle metabolism and renal function. As an example, in the vulnerable aged population correcting vitamin D deficiency may reduce its pleotropic negative effects including falls and fractures [92, 197–200]. Similarly, statin treatment may reduce risk of fractures, especially HF [154, 157, 201] alongside with beneficial effects on cardiovascular and CKD-related multimorbidity [202–204].

Treatment of coexisting and dynamically interrelated impaired renal function, musculoskeletal and other systemic diseases is complicated and challenging, especially in the advanced stages of CKD. The therapeutic role of antiresorptive medications in these patients remains is still debated [6, 23, 36, 62, 123, 185, 205–207]. In non-CKD populations, aminobisphosphonates, denosumab (a fully human monoclonal antibody that, by binding to receptor activator of nuclear factor kappa-B ligand (RANKL), prevents receptor activation of RANK and resulting in potent antiresorptive activity) and romosozumab (a humanized monoclonal antibody (IgG2) that binds to sclerostin and acts as an inhibitor), the major (first and second line) therapy in OP, have been shown to reduce OFs (HF—approximately by 40%, vertebral fracture by 45–70%, non-vertebral by 20-30%) [113, 121, 122, 208–215]), although the possible beneficial effects of anti-OP treatment among individuals with high fracture risk but limited life expectancy (e.g., the oldest nursing home residents) is controversial [216, 217]; in patients aged >75 years, anti-OP treatment did not reduce significantly the occurrence of HFs [218, 219]. In patients with CKD, these medications are also effective in improving BMD and reducing OFs, but there are uncertainties regarding their safety and efficacy in CKD G4-G5 [30, 31, 33–36, 206]. Anti-OP drugs slightly improve the BMD at the lumbar spine but not at the femoral neck; bisphosphonates may increase CKD progression (contraindicated if eGFR < 30 ml/min/1.73 $m^2$), whereas denosumab/romosozumab (not renally cleared drugs—[220, 221]) may induce hypocalcaemia. The osteoanabolic agents (PTH analogues—teriparatide and abaloparatide), currently restricted to a subpopulation at extremely high risk, are effective and safe in treatment of OP, including patients with CKD G1–G3 [with high risk for OP/OF] and normal endogenous PTH levels. In patients with CKD G4-G5 and adynamic bone disease such treatment is recommended to be considered on an individual basis [15, 36]. In general, antiresorptive agents should be administered in patients with a high bone turnover status and anabolic therapy (PTH analogues)—in those with low bone turnover disease. Some researchers propose early (in CKD stage (2) administration of PTH analogues to prevent hyperphosphatemia and FGF-23 level elevation, and, consequently, progression of CKD, bone-mineral disturbances, CVDs, and other related conditions [15].

On the other hand, it should be recognised that the ability of antiresorptive medications to control bone metabolism is not effective enough to prevent fractures,

especially non-vertebral fractures [205, 222, 223]. About 12% of patients in our HF cohort had been receiving anti-resorptive medications months pre-fracture. Clearly, current OP/OF management is suboptimal and there is an urgent need for new prevention and treatment options. The challenging interplay between renal function, CKD-related diseases (comorbidities), OP/OFs, advanced age (the greatest risk factor for all chronic diseases and poor outcomes), and medication used need to be addressed in each patient and the benefit/risk balance of any intervention assessed individually. A detailed discussion of the topic is beyond the scope of this paper and should be explored in future studies.

With ageing kidney, bone and muscle mass and function decline synchronically (in parallel with abnormalities in other organ systems) predisposing older persons to CKD, CVDs, and other chronic diseases, osteosarcopenia, falls, and fractures. Not surprisingly, the absolute CKD and HF burden is rising with population growth and ageing. A unified conceptual approach based on understanding and integrating the tight relations between CKD, OP, OF and comorbidities will help to choose and timely optimise individualised diagnostic, preventive and therapeutic actions, thus avoiding the devastating consequences of these diseases. Understandably, to alleviate the risk of OP and OF and to reduce the incidence of postoperative complications and deaths patients require holistic multidisciplinary care. Because CKD is both a result and driver of many diseases, most of which are known as risk factors for OP/OF, all physicians (geriatricians, nephrologists, endocrinologists, cardiologists, gastroenterologists, orthopaedic surgeons) and allied healthcare professionals should consider the CKD-musculoskeletal health interactions as an important clinical issue, to timely recognise and properly address patients with worsening kidney function.

On examination of an elderly person the following questions should be included and addressed: (1) what the renal function is, (2) which comorbidities may increase falls and fracture risk, (3) which diagnostic procedures should be used to stratify OP and OF risk, (4) what the adverse effects of prescribed medications are, and (5) what the optimal preventive and treatment strategy is. Considering that bone and muscle mass, renal and other organ systems synchronically decline with ageing predisposing older people to falls and OFs, optimising the treatment should include evidence-based personalised combined therapeutic approaches (physical activity, nutritional supplementation, and medications) addressing simultaneously and synergistically the individuals' constellation of diseases.

*4.7. Limitations and Strengths.* The study has several limitations that should be acknowledged. First, this was a single-centre observational cohort study and thus causality cannot be determined. Second, we did not analyse the confounding factors that can occur during surgery or postoperatively (e.g., bleeding, anaemia, infectious and thromboembolic complications, myocardial injury, etc.) and affect the outcomes. Third, our study population was mainly Caucasian (>97%) and limited to patients aged 65 years or older, therefore, the application of the described results and predictive models to other racial, ethnic, and age groups must be done with caution.

The strengths of this study include analysis of prospectively collected data on a relatively large cohort of consecutive HF patients treated in a tertiary academic university, assessment of a range of socio-demographic and clinical characteristics (40 variables) and use for prognostication of short-term outcomes only three simple and easily available at admission variables (CKD stage, age and one specific comorbidity), which enhance their utility and applicability.

## 5. Conclusions

Among older patients with HF, CKD is highly prevalent (39.9%). The CKD group (CKD stages G3–G5) has different clinical characteristics and outcomes, including a 2.5-fold higher mortality rate and 40% greater percentage of patients with prolonged LOS, but is rarely treated for OP. The strongest risk for an adverse outcome is advanced age (>80 years); the risk of a fatal event substantially increases in parallel with worsening kidney function, and especially in combination with CAD, or anaemia, or COPD, or AF, or dementia, or hyperparathyroidism, or vitamin D deficiency. Models based only on three variables at admission (CKD stage, age and one comorbid condition) predict in-hospital death with a reasonable degree of discrimination and accuracy. Assessment for renal function should be implemented in the standard clinical management of OP/OFs in all elderly patients.

## Data Availability

The original contributions presented in the study are included in the article, and further inquiries can be directed to the corresponding author.

## Ethical Approval

The study was conducted in accordance with the Declaration of Helsinki (1964) and the Council for International Organisations of Medical Sciences International Ethic Guidelines and approved by the Australian Capital Territory Human Research Ethics Committee (reference number: 2023.LRE.00063). Because the analysis was based on a digital anonymized database, the patients' written informed consent was waived.

## Disclosure

Part of this research has been presented at the Australian and New Zealand Society of Nephrology Annual Scientific Meeting 2022. (Jo-Wai Douglas Wang, Shyan Goh and Alexander Fisher—"Chronic Kidney Disease (CKD) in patients with osteoporotic hip fracture—prevalence, clinical profile, outcomes and management challenges," Australian and New Zealand Society of Nephrology Annual Scientific Meeting 2022, https://anznasm.com/15754).

## Conflicts of Interest

The authors declare that they have no conflicts of interest in this work (the study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflicts of interest).

## References


[1] Gbd Chronic Kidney Disease Collaboration, "Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017," *Lancet*, vol. 395, no. 10225, pp. 709–733, 2020.

[2] A. Levin, M. Tonelli, J. Bonventre et al., "Global kidney health 2017 and beyond: a roadmap for closing gaps in care, research, and policy," *The Lancet*, vol. 390, no. 10105, pp. 1888–1917, 2017.

[3] Y. Dong, Y. Zhang, K. Song, H. Kang, D. Ye, and F. Li, "What was the epidemiology and global burden of disease of hip fractures from 1990 to 2019? Results from and additional analysis of the global burden of disease study 2019," *Clinical Orthopaedics and Related Research*, vol. 481, no. 6, pp. 1209–1220, 2022.

[4] M. Bhandari and M. Swiontkowski, "Management of acute hip fracture," *New England Journal of Medicine*, vol. 377, no. 21, pp. 2053–2062, 2017.

[5] N. R. Hill, S. T. Fatoba, J. L. Oke et al., "Global prevalence of chronic kidney disease- A systematic review and meta-analysis," *PLoS One*, vol. 11, no. 7, Article ID 158765, 2016.

[6] T. Isakova, T. L. Nickolas, M. Denburg et al., "KDOQI US commentary on the 2017 KDIGO clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD)," *American Journal of Kidney Diseases*, vol. 70, no. 6, pp. 737–751, 2017.

[7] A. Pimentel, P. Ureña-Torres, M. C. Zillikens, J. Bover, and M. Cohen-Solal, "Fractures in patients with CKD-diagnosis, treatment, and prevention: a review by members of the European calcified tissue society and the European renal association of Nephrology dialysis and transplantation," *Kidney International*, vol. 92, no. 6, pp. 1343–1355, 2017.

[8] C. Castro-Alonso, L. D'Marco, J. Pomes et al., "Prevalence of vertebral fractures and their prognostic significance in the survival in patients with chronic kidney disease stages 3–5 not on dialysis," *Journal of Clinical Medicine*, vol. 9, no. 5, p. 1604, 2020.

[9] P. Evenepoel, J. Cunningham, S. Ferrari et al., "European Consensus Statement on the diagnosis and management of osteoporosis in chronic kidney disease stages G4-G5D," *Nephrology Dialysis Transplantation*, vol. 36, no. 1, pp. 42–59, 2021.

[10] A. Pimentel, P. Ureña-Torres, J. Bover, J. Luis Fernandez-Martín, and M. Cohen-Solal, "Bone fragility fractures in CKD patients," *Calcified Tissue International*, vol. 108, no. 4, pp. 539–550, 2021.

[11] C. P. Kovesdy, "Epidemiology of chronic kidney disease: an update 2022," *Kidney International Supplements*, vol. 12, no. 1, pp. 7–11, 2022.

[12] Y. El Miedany, N. A. Gadallah, E. Sarhan et al., "Consensus evidence-based clinical practice recommendations for the diagnosis and treat-to-target management of osteoporosis in chronic kidney disease stages G4-g5d and post-transplantation: an initiative of Egyptian academy of bone health," *Kidney Disease*, vol. 8, no. 5, pp. 392–407, 2022.

[13] I. J. A. de Bruin, C. E. Wyers, P. C. Souverein et al., "The risk of new fragility fractures in patients with chronic kidney disease and hip fracture-a population-based cohort study in the UK," *Osteoporosis International*, vol. 31, no. 8, pp. 1487–1497, 2020.

[14] C. Y. Hsu, L. R. Chen, and K. H. Chen, "Osteoporosis in patients with chronic kidney diseases: a systemic review," *International Journal of Molecular Sciences*, vol. 21, no. 18, p. 6846, 2020.

[15] M. Pazianas and P. D. Miller, "Osteoporosis and chronic kidney disease-mineral and bone disorder (CKD-MBD): back to basics," *American Journal of Kidney Diseases*, vol. 78, no. 4, pp. 582–589, 2021.

[16] P. D. Miller, "Chronic kidney disease and the skeleton," *Bone Res.*, vol. 2, no. 1, Article ID 14044, 2014.

[17] X. H. Wang, W. E. Mitch, and S. R. Price, "Pathophysiological mechanisms leading to muscle loss in chronic kidney disease," *Nature Reviews Nephrology*, vol. 18, no. 3, pp. 138–152, 2022.

[18] K. A. Jenkin and B. D. Perry, "Skeletal muscle and kidney crosstalk in chronic kidney disease," *Cellular Physiology and Biochemistry*, vol. 56, no. 5, pp. 587–601, 2022.

[19] L. Hu, A. Napoletano, M. Provenzano et al., "Mineral bone disorders in kidney disease patients: the ever-current topic," *International Journal of Molecular Sciences*, vol. 23, no. 20, Article ID 12223, 2022.

[20] E. Bellorin-Font, E. Rojas, and K. J. Martin, "Bone disease in chronic kidney disease and kidney transplant," *Nutrients*, vol. 15, no. 1, p. 167, 2022.

[21] M. P. Duarte, H. S. Ribeiro, S. G. R. Neri et al., "Prevalence of low bone mineral density (T-score ≤- 2.5) in the whole spectrum of chronic kidney disease: a systematic review and meta-analysis," *Osteoporosis International*, vol. 34, no. 3, pp. 467–477, 2023.

[22] K. L. Naylor, E. McArthur, W. D. Leslie et al., "The three-year incidence of fracture in chronic kidney disease," *Kidney International*, vol. 86, no. 4, pp. 810–818, 2014.

[23] S. M. Moe and T. L. Nickolas, "Fractures in patients with CKD: time for action," *Clinical Journal of the American Society of Nephrology*, vol. 11, no. 11, pp. 1929–1931, 2016.

[24] T. Vilaca, S. Salam, M. Schini et al., "Risks of hip and nonvertebral fractures in patients with CKD g3a-g5d: a systematic review and meta-analysis," *American Journal of Kidney Diseases*, vol. 76, no. 4, pp. 521–532, 2020.

[25] M. Covino, R. Vitiello, G. De Matteis et al., "Hip fracture risk in elderly with non-end-stage chronic kidney disease: a fall related analysis," *The American Journal of the Medical Sciences*, vol. 363, no. 1, pp. 48–54, 2022.

[26] S. K. Khan, S. P. Rushton, M. Courtney, A. C. Gray, and D. J. Deehan, "Elderly men with renal dysfunction are most at risk for poor outcome after neck of femur fractures," *Age and Ageing*, vol. 42, no. 1, pp. 76–81, 2013.

[27] Y. Meng, M. Fu, J. Guo, Z. Wang, Y. Zhang, and Z. Hou, "Characteristics and complications of fracture in older adults with chronic kidney disease: a cross-sectional study," *Journal of Orthopaedic Surgery and Research*, vol. 17, no. 1, p. 377, 2022.

[28] H. M. Pajulammi, T. H. Luukkaala, H. K. Pihlajamäki, and M. S. Nuotio, "Decreased glomerular filtration rate estimated by 2009 CKD-EPI equation predicts mortality in older hip fracture population," *Injury*, vol. 47, no. 7, pp. 1536–1542, 2016.

[29] G. E. Vigni, F. Bosco, A. Cioffi, and L. Camarda, "Mortality risk assessment at the admission in patient with proximal

femur fractures: electrolytes and renal function," *Geriatric Orthopaedic Surgery and Rehabilitation*, vol. 12, Article ID 2151459321991503, 2021.

[30] H. Yun, E. Delzell, K. G. Saag et al., "Fractures and mortality in relation to different osteoporosis treatments," *Clinical and Experimental Rheumatology*, vol. 33, no. 3, pp. 302–309, 2015.

[31] T. Hara, Y. Hijikata, and Y. Matsubara, "Effectiveness of pharmacological interventions versus placebo or No treatment for osteoporosis in patients with CKD stages 3-5D: editorial summary of a cochrane review," *American Journal of Kidney Diseases*, vol. 80, no. 6, pp. 794–796, 2022.

[32] W. J. Deardorff, I. Cenzer, B. Nguyen, and S. J. Lee, "Time to benefit of bisphosphonate therapy for the prevention of fractures among postmenopausal women with osteoporosis: a meta-analysis of randomized clinical trials," *JAMA Internal Medicine*, vol. 182, no. 1, pp. 33–41, 2022.

[33] C. Ginsberg and J. H. Ix, "Diagnosis and management of osteoporosis in advanced kidney disease: a review," *American Journal of Kidney Diseases*, vol. 79, no. 3, pp. 427–436, 2022.

[34] G. Iolascon and A. Moretti, "What are the efficacy and safety of pharmacological interventions versus placebo, no treatment or usual care for osteoporosis in people with chronic kidney disease stages 3-5D?- A Cochrane Review summary with commentary," *Journal of Musculoskeletal and Neuronal Interactions*, vol. 22, no. 1, pp. 1–4, 2022.

[35] P. D. Miller, J. D. Adachi, B. H. Albergaria et al., "Efficacy and safety of romosozumab among postmenopausal women with osteoporosis and mild-to-moderate chronic kidney disease," *Journal of Bone and Mineral Research*, vol. 37, no. 8, pp. 1437–1445, 2022.

[36] M. Haarhaus, L. Aaltonen, D. Cejka et al., "Management of fracture risk in CKD-traditional and novel approaches," *Clinical Kidney Journal*, vol. 16, no. 3, pp. 456–472, 2023.

[37] A. S. Levey, L. A. Stevens, C. H. Schmid et al., "A new equation to estimate glomerular filtration rate," *Annals of Internal Medicine*, vol. 150, no. 9, pp. 604–612, 2009.

[38] Australian Bureau of Statistics, "Australian health survey: biomedical results for chronic diseases, 2011-12 financial year," 2013, https://www.abs.gov.au/methodologies/australianhealth-survey-biomedical-results-chronic-diseases-methodology/2011-12.

[39] Australian Bureau of Statistics, "National health survey: first results, 2017-2018 financial year," 2015, https://www.abs.gov.au/statistics/health/health-conditions-and-risks/national-healthsurvey/2017-18.

[40] Australian Bureau of Statistics, "National health survey: first results, 2017-2018 financial year," 2018, https://www.abs.gov.au/statistics/health/health-conditions-and-risks/national-healthsurvey/2017-18.

[41] S. Linn and P. D. Grunau, "New patient-oriented summary measure of net total gain in certainty for dichotomous diagnostic tests," *Epidemiologic Perspectives and Innovations*, vol. 3, no. 1, p. 11, 2006.

[42] A. J. Larner, "Number needed to diagnose, predict, or misdiagnose: useful metrics for non-canonical signs of cognitive status?" *Dementia and Geriatric Cognitive Disorders Extra*, vol. 8, no. 3, pp. 321–327, 2018.

[43] G. Nattino, M. L. Pennell, and S. Lemeshow, "Assessing the goodness of fit of logistic regression models in large samples: a modification of the Hosmer-Lemeshow test," *Biometrics*, vol. 76, no. 2, pp. 549–560, 2020.

[44] C. R. Harris, K. J. Millman, S. J. van der Walt et al., "Array programming with NumPy," *Nature*, vol. 585, no. 7825, pp. 357–362, 2020.

[45] P. Virtanen, R. Gommers, T. E. Oliphant et al., "SciPy 1.0: fundamental algorithms for scientific computing in Python," *Nature Methods*, vol. 17, no. 3, pp. 261–272, 2020.

[46] McK. Wo, "Data structures for statistical computing in Python. Proceedings of the 9th Python in science conference," in *Proceedings of the Python in Science Conference*, Austin, TX, USA, July 2010.

[47] R Core Development Team, *R: A Language and Environment for Statistical Computing*, R Foundation for Statistical Computing, Vienna, Austria, 2022.

[48] J. Radford, A. Kitsos, J. Stankovich et al., "Epidemiology of chronic kidney disease in Australian general practice: national Prescribing Service MedicineWise MedicineInsight dataset," *Nephrology*, vol. 24, no. 10, pp. 1017–1025, 2019.

[49] A. M. Alem, D. J. Sherrard, D. L. Gillen et al., "Increased risk of hip fracture among patients with end-stage renal disease," *Kidney International*, vol. 58, no. 1, pp. 396–399, 2000.

[50] L. Dukas, E. Schacht, and H. B. Stähelin, "In elderly men and women treated for osteoporosis a low creatinine clearance of <65 ml/min is a risk factor for falls and fractures," *Osteoporosis International*, vol. 16, no. 12, pp. 1683–1690, 2005.

[51] T. L. Nickolas, D. J. McMahon, and E. Shane, "Relationship between moderate to severe kidney disease and hip fracture in the United States," *Journal of the American Society of Nephrology*, vol. 17, no. 11, pp. 3223–3232, 2006.

[52] A. C. Dooley, N. S. Weiss, and B. Kestenbaum, "Increased risk of hip fracture among men with CKD," *American Journal of Kidney Diseases*, vol. 51, no. 1, pp. 38–44, 2008.

[53] K. E. Ensrud, "Fracture risk in CKD," *Clinical Journal of the American Society of Nephrology*, vol. 8, no. 8, pp. 1282-1283, 2013.

[54] H. Chen, P. Lips, M. G. Vervloet, N. M. van Schoor, and R. T. de Jongh, "Association of renal function with bone mineral density and fracture risk in the Longitudinal Aging Study Amsterdam," *Osteoporosis International*, vol. 29, no. 9, pp. 2129–2138, 2018.

[55] N. A. Goto, A. C. G. Weststrate, F. M. Oosterlaan et al., "The association between chronic kidney disease, falls, and fractures: a systematic review and meta-analysis," *Osteoporosis International*, vol. 31, no. 1, pp. 13–29, 2020.

[56] L. F. Fried, M. L. Biggs, M. G. Shlipak et al., "Association of kidney function with incident hip fracture in older adults," *Journal of the American Society of Nephrology*, vol. 18, no. 1, pp. 282–286, 2007.

[57] T. J. Arneson, S. Li, J. Liu, R. D. Kilpatrick, B. B. Newsome, and W. L. St Peter, "Trends in hip fracture rates in US hemodialysis patients, 1993-2010," *American Journal of Kidney Diseases*, vol. 62, no. 4, pp. 747–754, 2013.

[58] S. S. Nair, A. A. Mitani, B. A. Goldstein, G. M. Chertow, D. W. Lowenberg, and W. C. Winkelmayer, "Temporal trends in the incidence, treatment, and outcomes of hip fracture in older patients initiating dialysis in the United States," *Clinical Journal of the American Society of Nephrology*, vol. 8, no. 8, pp. 1336–1342, 2013.

[59] K. E. Ensrud, N. Parimi, H. A. Fink et al., "Estimated GFR and risk of hip fracture in older men: comparison of associations using cystatin C and creatinine," *American Journal of Kidney Diseases*, vol. 63, no. 1, pp. 31–39, 2014.

[60] M. J. Pérez-Sáez, D. Prieto-Alhambra, C. Barrios et al., "Increased hip fracture and mortality in chronic kidney

disease individuals: the importance of competing risks," *Bone*, vol. 73, pp. 154–159, 2015.

[61] B. Runesson, M. Trevisan, K. Iseri et al., "Fractures and their sequelae in non-dialysis-dependent chronic kidney disease: the Stockholm CREAtinine Measurement project," *Nephrology Dialysis Transplantation*, vol. 35, no. 11, pp. 1908–1915, 2020.

[62] D. Hauck, L. Nery, R. O'Connell, R. Clifton-Bligh, A. Mather, and C. M. Girgis, "Bisphosphonates and bone mineral density in patients with end-stage kidney disease and renal transplants: a 15-year single-centre experience," *BoneKEy Reports*, vol. 16, Article ID 101178, 2022.

[63] S. A. Jamal, "Bone mass measurements in men and women with chronic kidney disease," *Current Opinion in Nephrology and Hypertension*, vol. 19, no. 4, pp. 343–348, 2010.

[64] M. J. Elliott, M. T. James, R. R. Quinn et al., "Estimated GFR and fracture risk: a population-based study," *Clinical Journal of the American Society of Nephrology*, vol. 8, no. 8, pp. 1367–1376, 2013.

[65] B. Abrahamsen, T. van Staa, R. Ariely, M. Olson, and C. Cooper, "Excess mortality following hip fracture: a systematic epidemiological review," *Osteoporosis International*, vol. 20, no. 10, pp. 1633–1650, 2009.

[66] K. Singh Mangat, A. Mehra, I. Yunas, P. Nightingale, and K. Porter, "Is estimated peri-operative glomerular filtration rate associated with post-operative mortality in fractured neck of femur patients?" *Injury*, vol. 39, no. 10, pp. 1141–1146, 2008.

[67] D. Nitsch, A. Mylne, P. J. Roderick, L. Smeeth, R. Hubbard, and A. Fletcher, "Chronic kidney disease and hip fracture-related mortality in older people in the UK," *Nephrology Dialysis Transplantation*, vol. 24, no. 5, pp. 1539–1544, 2009.

[68] F. Hu, C. Jiang, J. Shen, P. Tang, and Y. Wang, "Preoperative predictors for mortality following hip fracture surgery: a systematic review and meta-analysis," *Injury*, vol. 43, no. 6, pp. 676–685, 2012.

[69] C. López-Martínez, E. Tovar-Rivera, I. K. Becerra-Laparra, and N. C. Chávez-Tapia, "Clinical impact of indirect markers of renal function in elderly patients with hip fracture," *Geriatric Orthopaedic Surgery and Rehabilitation*, vol. 5, no. 3, pp. 131–137, 2014.

[70] T. Gulin, I. Kruljac, L. Kirigin et al., "Advanced age, high $\beta$-CTX levels, and impaired renal function are independent risk factors for all-cause one-year mortality in hip fracture patients," *Calcified Tissue International*, vol. 98, no. 1, pp. 67–75, 2016.

[71] Y. S. Suh, S. H. Won, H. S. Choi et al., "Survivorship and complications after hip fracture surgery in patients with chronic kidney disease," *Journal of Korean Medical Science*, vol. 32, no. 12, pp. 2035–2041, 2017.

[72] Y. Komorita, M. Iwase, Y. Idewaki et al., "Impact of hip fracture on all-cause mortality in Japanese patients with type 2 diabetes mellitus: the Fukuoka Diabetes Registry," *Journal of Diabetes Investigation*, vol. 11, no. 1, pp. 62–69, 2020.

[73] P. Ramamurti, S. C. Fassihi, D. Sacolick, A. Gu, C. Wei, and M. D. Chodos, "Impaired renal function is an independent risk factor for complications after surgery for femoral neck fracture," *HIP International*, vol. 33, no. 2, pp. 345–353, 2023.

[74] C. Ongzalima, K. Dasborough, S. Narula, G. Boardman, P. Kumarasinghe, and H. Seymour, "Perioperative management and outcomes of hip fracture patients with advanced chronic kidney disease," *Geriatric Orthopaedic Surgery and Rehabilitation*, vol. 13, Article ID 21514593221138658, 2022.

[75] D. Roy, S. Pande, S. Thalanki et al., "Hip fractures in elderly patients with non-dialysis dependent chronic kidney disease: outcomes in a Southeast Asian population," *Medicine (Baltimore)*, vol. 100, no. 27, Article ID e26625, 2021.

[76] L. Robertson, C. Black, N. Fluck et al., "Hip fracture incidence and mortality in chronic kidney disease: the GLOMMS-II record linkage cohort study," *BMJ Open*, vol. 8, no. 4, Article ID e020312, 2018.

[77] O. A. Phruetthiphat, S. Paiboonrungroj, Y. Satravaha, and A. Lawanprasert, "The effect of CKD on intertrochanteric fracture treated with proximal femoral nail anti-rotation: a 7-year study," *Journal of Orthopaedics*, vol. 32, pp. 151–155, 2022.

[78] S. Gaddam, S. K. Gunukula, J. W. Lohr, and P. Arora, "Prevalence of chronic kidney disease in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis," *BMC Pulmonary Medicine*, vol. 16, no. 1, p. 158, 2016.

[79] P. A. McCullough, "Anemia of cardiorenal syndrome," *Kidney International Supplements*, vol. 11, no. 1, pp. 35–45, 2021.

[80] M. J. Williams, S. C. White, Z. Joseph, and K. A. Hruska, "Updates in the chronic kidney disease-mineral bone disorder show the role of osteocytic proteins, a potential mechanism of the bone-Vascular paradox, a therapeutic target, and a biomarker," *Frontiers in Physiology*, vol. 14, Article ID 1120308, 2023.

[81] G. M. Virzì, A. Clementi, A. Brocca et al., "The hemodynamic and nonhemodynamic crosstalk in cardiorenal syndrome type 1," *Cardiorenal Medicine*, vol. 4, no. 2, pp. 103–112, 2014.

[82] A. Gupta, K. Kennedy, J. Perales-Puchalt et al., "Mild-moderate CKD is not associated with cognitive impairment in older adults in the Alzheimer's Disease Neuroimaging Initiative cohort," *PLoS One*, vol. 15, no. 10, Article ID e0239871, 2020.

[83] B. Afsar, A. A. Sag, C. E. Yalcin et al., "Brain-kidney cross-talk: definition and emerging evidence," *European Journal of Internal Medicine*, vol. 36, pp. 7–12, 2016.

[84] C. Y. Zhang, F. F. He, H. Su, C. Zhang, and X. F. Meng, "Association between chronic kidney disease and Alzheimer's disease: an update," *Metabolic Brain Disease*, vol. 35, no. 6, pp. 883–894, 2020.

[85] J. Y. Kong, J. S. Kim, M. H. Kang, H. S. Hwang, C. W. Won, and K. H. Jeong, "Renal dysfunction is associated with decline of cognitive function in community-dwelling older adults: Korean frailty and aging cohort study," *BMC Geriatrics*, vol. 20, no. 1, p. 462, 2020.

[86] C. F. Lin, H. C. Liu, and S. Y. Lin, "Kidney function and risk of physical and cognitive impairment in older persons with type 2 diabetes at an outpatient clinic with geriatric assessment implementation," *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, vol. 15, pp. 79–91, 2022.

[87] M. Grasing, P. Sharma, R. J. Lepping et al., "Association between the estimated glomerular filtration rate and brain atrophy in older adults," *American Journal of Nephrology*, vol. 53, no. 2-3, pp. 176–181, 2022.

[88] T. Yoshizawa, K. Okada, S. Furuichi et al., "Prevalence of chronic kidney diseases in patients with chronic obstructive pulmonary disease: assessment based on glomerular filtration rate estimated from creatinine and cystatin C levels,"

*International Journal of Chronic Obstructive Pulmonary Disease*, vol. 10, pp. 1283–1289, 2015.

[89] C. Tebé, D. Martinez-Laguna, V. Moreno et al., "Differential mortality and the excess rates of hip fracture associated with type 2 diabetes: accounting for competing risks in fracture prediction matters," *Journal of Bone and Mineral Research*, vol. 33, no. 8, pp. 1417–1421, 2018.

[90] A. S. Go, G. M. Chertow, D. Fan, C. E. McCulloch, and C. Y. Hsu, "Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization," *New England Journal of Medicine*, vol. 351, no. 13, pp. 1296–1305, 2004.

[91] J. I. Barzilay, P. Buzkova, J. A. Cauley, J. A. Robbins, H. A. Fink, and K. J. Mukamal, "The associations of subclinical atherosclerotic cardiovascular disease with hip fracture risk and bone mineral density in elderly adults," *Osteoporosis International*, vol. 29, no. 10, pp. 2219–2230, 2018.

[92] T. K. Young, N. D. Toussaint, G. L. Di Tanna et al., "Risk factors for fracture in patients with coexisting chronic kidney disease and type 2 diabetes: an observational analysis from the CREDENCE trial," *Journal of Diabetes Research*, vol. 2022, Article ID 9998891, 12 pages, 2022.

[93] K. Matsushita, S. H. Ballew, A. Y. Wang, R. Kalyesubula, E. Schaeffner, and R. Agarwal, "Epidemiology and risk of cardiovascular disease in populations with chronic kidney disease," *Nature Reviews Nephrology*, vol. 18, no. 11, pp. 696–707, 2022.

[94] E. Ku, B. J. Lee, J. Wei, and M. R. Weir, "Hypertension in CKD: core curriculum 2019," *American Journal of Kidney Diseases*, vol. 74, no. 1, pp. 120–131, 2019.

[95] O. Buyadaa, A. Salim, J. I. Morton, K. Jandeleit-Dahm, D. J. Magliano, and J. E. Shaw, "Examining the factors contributing to the association between non-albuminuric CKD and a low rate of kidney function decline in diabetes," *Therapeutic Advances in Endocrinology and Metabolism*, vol. 13, Article ID 20420188221083518, 2022.

[96] O. Z. Ameer, "Hypertension in chronic kidney disease: what lies behind the scene," *Frontiers in Pharmacology*, vol. 13, Article ID 949260, 2022.

[97] F. C. Trudzinski, M. Alqudrah, A. Omlor et al., "Consequences of chronic kidney disease in chronic obstructive pulmonary disease," *Respiratory Research*, vol. 20, no. 1, p. 151, 2019.

[98] N. Madouros, S. Jarvis, A. Saleem, E. Koumadoraki, S. Sharif, and S. Khan, "Is there an association between chronic obstructive pulmonary disease and chronic renal failure?" *Cureus*, vol. 14, no. 6, Article ID e26149, 2022.

[99] C. G. Moran, R. T. Wenn, M. Sikand, and A. M. Taylor, "Early mortality after hip fracture: is delay before surgery important?" *The Journal of Bone and Joint Surgery*, vol. 87, no. 3, pp. 483–489, 2005.

[100] D. Bliuc, N. D. Nguyen, V. E. Milch, T. V. Nguyen, J. A. Eisman, and J. R. Center, "Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women," *JAMA*, vol. 301, no. 5, pp. 513–521, 2009.

[101] P. Haentjens, J. Magaziner, C. S. Colón-Emeric et al., "Meta-analysis: excess mortality after hip fracture among older women and men," *Annals of Internal Medicine*, vol. 152, no. 6, pp. 380–390, 2010.

[102] R. S. Sterling, "Gender and race/ethnicity differences in hip fracture incidence, morbidity, mortality, and function," *Clinical Orthopaedics and Related Research*, vol. 469, no. 7, pp. 1913–1918, 2011.

[103] S. Y. Jang, Y. Cha, N. K. Park, K. J. Kim, and W. S. Choy, "Effect modification on death by age and sex in elderly hip fracture," *J Bone Metab*, vol. 29, no. 4, pp. 235–243, 2022.

[104] J. Neugarten and L. Golestaneh, "Influence of sex on the progression of chronic kidney disease," *Mayo Clinic Proceedings*, vol. 94, no. 7, pp. 1339–1356, 2019.

[105] A. C. Ricardo, W. Yang, D. Sha et al., "Sex-related disparities in CKD progression," *Journal of the American Society of Nephrology*, vol. 30, no. 1, pp. 137–146, 2019.

[106] S. R. Cummings, L. Y. Lui, R. Eastell, and I. E. Allen, "Association between drug treatments for patients with osteoporosis and overall mortality rates: a meta-analysis," *JAMA Internal Medicine*, vol. 179, no. 11, pp. 1491–1500, 2019.

[107] K. W. Lyles, C. S. Colón-Emeric, J. S. Magaziner et al., "Zoledronic acid and clinical fractures and mortality after hip fracture," *New England Journal of Medicine*, vol. 357, no. 18, pp. 1799–1809, 2007.

[108] P. N. Sambrook, I. D. Cameron, J. S. Chen et al., "Oral bisphosphonates are associated with reduced mortality in frail older people: a prospective five-year study," *Osteoporosis International*, vol. 22, no. 9, pp. 2551–2556, 2011.

[109] J. R. Center, D. Bliuc, N. D. Nguyen, T. V. Nguyen, and J. A. Eisman, "Osteoporosis medication and reduced mortality risk in elderly women and men," *Journal of Clinical Endocrinology and Metabolism*, vol. 96, no. 4, pp. 1006–1014, 2011.

[110] L. Bondo, P. Eiken, and B. Abrahamsen, "Analysis of the association between bisphosphonate treatment survival in Danish hip fracture patients-a nationwide register-based open cohort study," *Osteoporosis International*, vol. 24, no. 1, pp. 245–252, 2013.

[111] W. Brozek, B. Reichardt, J. Zwerina, H. P. Dimai, K. Klaushofer, and E. Zwettler, "Antiresorptive therapy and risk of mortality and refracture in osteoporosis-related hip fracture: a nationwide study," *Osteoporosis International*, vol. 27, no. 1, pp. 387–396, 2016.

[112] D. Bliuc, T. Tran, T. van Geel et al., "Mortality risk reduction differs according to bisphosphonate class: a 15-year observational study," *Osteoporosis International*, vol. 30, no. 4, pp. 817–828, 2019.

[113] P. W. Wang, Y. Z. Li, H. F. Zhuang et al., "Anti-osteoporosis medications associated with decreased mortality after hip fracture," *Orthopaedic Surgery*, vol. 11, no. 5, pp. 777–783, 2019.

[114] P. Lee, C. Ng, A. Slattery, P. Nair, J. A. Eisman, and J. R. Center, "Preadmission bisphosphonate and mortality in critically ill patients," *Journal of Clinical Endocrinology and Metabolism*, vol. 101, no. 5, pp. 1945–1953, 2016.

[115] T. W. Tai, J. S. Hwang, C. C. Li, J. C. Hsu, C. W. Chang, and C. H. Wu, "The impact of various anti-osteoporosis drugs on all-cause mortality after hip fractures: a nationwide population study," *Journal of Bone and Mineral Research*, vol. 37, no. 8, pp. 1520–1526, 2022.

[116] C. H. Wu, C. C. Li, Y. H. Hsu, F. W. Liang, Y. F. Chang, and J. S. Hwang, "Comparisons between different anti-osteoporosis medications on postfracture mortality: a population-based study," *Journal of Clinical Endocrinology and Metabolism*, vol. 108, no. 4, pp. 827–833, 2023.

[117] X. Wang, C. Li, Y. He et al., "Anti-osteoporosis medication treatment pattern after osteoporotic fracture during 2010-2016 in Fujian, China," *Archives of Osteoporosis*, vol. 15, no. 1, p. 134, 2020.

[118] F. Lombardi, L. Paoletti, B. Carrieri et al., "Underprescription of medications in older adults: causes, consequences and solutions-a narrative review," *Eur Geriatr Med*, vol. 12, no. 3, pp. 453–462, 2021.

[119] D. Bliuc, T. Tran, W. Chen et al., "The association between multimorbidity and osteoporosis investigation and treatment in high-risk fracture patients in Australia: a prospective cohort study," *PLoS Medicine*, vol. 20, no. 1, Article ID e1004142, 2023.

[120] H. Hagino, Y. Yoshinaga, E. Hamaya, T. C. Lin, M. Ajmera, and J. Meyers, "A real-world study of treatment patterns among patients with osteoporotic fracture: analysis of a Japanese hospital database," *Archives of Osteoporosis*, vol. 18, no. 1, p. 23, 2023.

[121] R. Rizzoli, O. Bruyere, J. B. Cannata-Andia et al., "Management of osteoporosis in the elderly," *Current Medical Research and Opinion*, vol. 25, no. 10, pp. 2373–2387, 2009.

[122] L. Degli Esposti, A. Girardi, S. Saragoni et al., "Use of antiosteoporotic drugs and calcium/vitamin D in patients with fragility fractures: impact on re-fracture and mortality risk," *Endocrine*, vol. 64, no. 2, pp. 367–377, 2019.

[123] M. Abdalbary, M. Sobh, S. Elnagar et al., "Management of osteoporosis in patients with chronic kidney disease," *Osteoporosis International*, vol. 33, no. 11, pp. 2259–2274, 2022.

[124] S. Khosla, J. A. Cauley, J. Compston et al., "Addressing the crisis in the treatment of osteoporosis: a path forward," *Journal of Bone and Mineral Research*, vol. 32, no. 3, pp. 424–430, 2017.

[125] O. Guzon-Illescas, E. Perez Fernandez, N. Crespí Villarias et al., "Mortality after osteoporotic hip fracture: incidence, trends, and associated factors," *Journal of Orthopaedic Surgery and Research*, vol. 14, no. 1, p. 203, 2019.

[126] P. Cockwell and L. A. Fisher, "The global burden of chronic kidney disease," *The Lancet*, vol. 395, no. 10225, pp. 662–664, 2020.

[127] M. Fiorentino, D. Bolignano, V. Tesar et al., "Renal biopsy in patients with diabetes: a pooled meta-analysis of 48 studies," *Nephrology Dialysis Transplantation*, vol. 32, no. 1, pp. 97–110, 2017.

[128] N. Prasad, V. Veeranki, D. Bhadauria et al., "Non-diabetic kidney disease in type 2 diabetes mellitus: a changing spectrum with therapeutic ascendancy," *Journal of Clinical Medicine*, vol. 12, no. 4, p. 1705, 2023.

[129] S. Singh, P. S. Patel, and A. Archana, "Heterogeneity in kidney histology and its clinical indicators in type 2 diabetes mellitus: a retrospective study," *Journal of Clinical Medicine*, vol. 12, no. 5, p. 1778, 2023.

[130] M. Simonini and G. Vezzoli, "New landmarks to slow the progression of chronic kidney disease," *Journal of Clinical Medicine*, vol. 12, no. 1, p. 2, 2022.

[131] M. Tonelli, N. Wiebe, B. Guthrie et al., "Comorbidity as a driver of adverse outcomes in people with chronic kidney disease," *Kidney International*, vol. 88, no. 4, pp. 859–866, 2015.

[132] S. D. Fraser and M. W. Taal, "Multimorbidity in people with chronic kidney disease: implications for outcomes and treatment," *Current Opinion in Nephrology and Hypertension*, vol. 25, no. 6, pp. 465–472, 2016.

[133] S. J. Duffield, B. M. Ellis, N. Goodson et al., "The contribution of musculoskeletal disorders in multimorbidity: implications for practice and policy," *Best Practice and Research Clinical Rheumatology*, vol. 31, no. 2, pp. 129–144, 2017.

[134] H. S. Jørgensen, K. David, S. Salam, and P. Evenepoel, "Traditional and non-traditional risk factors for osteoporosis in CKD," *Calcified Tissue International*, vol. 108, no. 4, pp. 496–511, 2021.

[135] A. Barcelos, D. G. Lopes, H. Canhão, J. da Cunha Branco, and A. M. Rodrigues, "Multimorbidity is associated with fragility fractures in women 50 years and older: a nationwide cross-sectional study," *BoneKEy Reports*, vol. 15, Article ID 101139, 2021.

[136] H. Kimura, K. Tanaka, H. Saito et al., "Association of polypharmacy with incidence of CKD: a retrospective cohort study," *Clinical and Experimental Nephrology*, vol. 27, no. 3, pp. 272–278, 2023.

[137] G. Hawthorne, C. J. Lightfoot, A. C. Smith, K. Khunti, and T. J. Wilkinson, "Multimorbidity prevalence and patterns in chronic kidney disease: findings from an observational multicentre UK cohort study," *International Urology and Nephrology*, vol. 55, no. 8, pp. 2047–2057, 2023.

[138] C. B. Bowling, L. Plantinga, L. S. Phillips et al., "Association of multimorbidity with mortality and healthcare utilization in chronic kidney disease," *Journal of the American Geriatrics Society*, vol. 65, no. 4, pp. 704–711, 2017.

[139] R. de Filippis, M. Mercurio, G. Spina et al., "Antidepressants and vertebral and hip risk fracture: an updated systematic review and meta-analysis," *Healthcare*, vol. 10, no. 5, p. 803, 2022.

[140] M. Mercurio, R. de Filippis, G. Spina et al., "The use of antidepressants is linked to bone loss: a systematic review and metanalysis," *Orthopedic Reviews*, vol. 14, no. 6, Article ID 38564, 2022.

[141] S. J. Mortensen, A. Mohamadi, C. L. Wright et al., "Medications as a risk factor for fragility hip fractures: a systematic review and meta-analysis," *Calcified Tissue International*, vol. 107, no. 1, pp. 1–9, 2020.

[142] M. W. Cole, T. L. Waters, L. K. Collins et al., "How do the top 10 known offending drug classes associated with decreased bone mineral density affect total shoulder arthroplasty outcomes?" *Journal of Shoulder and Elbow Surgery*, vol. 32, no. 5, pp. 1009–1015, 2023.

[143] M. Solmi, A. Murru, I. Pacchiarotti et al., "Safety, tolerability, and risks associated with first- and second-generation antipsychotics: a state-of-the-art clinical review," *Therapeutics and Clinical Risk Management*, vol. 13, pp. 757–777, 2017.

[144] N. H. Gonsai, V. H. Amin, C. G. Mendpara, R. Speth, and G. M. Hale, "Effects of dopamine receptor antagonist antipsychotic therapy on blood pressure," *Journal of Clinical Pharmacy and Therapeutics*, vol. 43, no. 1, pp. 1–7, 2018.

[145] M. Højlund, L. C. Lund, J. L. E. Herping, M. B. Haastrup, P. Damkier, and D. P. Henriksen, "Second-generation antipsychotics and the risk of chronic kidney disease: a population-based case-control study," *BMJ Open*, vol. 10, no. 8, Article ID e038247, 2020.

[146] J. J. Damba, K. Bodenstein, P. Lavin et al., "Psychotropic drugs and adverse kidney effects: a systematic review of the past decade of research," *CNS Drugs*, vol. 36, no. 10, pp. 1049–1077, 2022.

[147] M. Urquiaga and K. G. Saag, "Risk for osteoporosis and fracture with glucocorticoids," *Best Practice and Research Clinical Rheumatology*, vol. 36, no. 3, Article ID 101793, 2022.

[148] L. C. Desbiens, N. Khelifi, Y. P. Wang et al., "Thiazide diuretics and fracture risk: a systematic review and meta-analysis of randomized clinical trials," *JBMR Plus*, vol. 6, no. 11, Article ID e10683, 2022.

[149] L. Fisher, A. Fisher, and P. N. Smith, "*Helicobacter pylori* related diseases and osteoporotic fractures (narrative

review)," *Journal of Clinical Medicine*, vol. 9, no. 10, p. 3253, 2020.

[150] A. C. van der Burgh, C. E. de Keyser, M. C. Zillikens, and B. H. Stricker, "The effects of osteoporotic and non-osteoporotic medications on fracture risk and bone mineral density," *Drugs*, vol. 81, no. 16, pp. 1831–1858, 2021.

[151] M. Velliou, E. Sanidas, A. Zografou, D. Papadopoulos, N. Dalianis, and J. Barbetseas, "Antihypertensive drugs and risk of bone fractures," *Drugs and Aging*, vol. 39, no. 7, pp. 551–557, 2022.

[152] J. Lee, A. Negm, R. Peters, E. K. C. Wong, and A. Holbrook, "Deprescribing fall-risk increasing drugs (FRIDs) for the prevention of falls and fall-related complications: a systematic review and meta-analysis," *BMJ Open*, vol. 11, no. 2, Article ID e035978, 2021.

[153] J. Makovey, J. S. Chen, C. Hayward, F. M. Williams, and P. N. Sambrook, "Association between serum cholesterol and bone mineral density," *Bone*, vol. 44, no. 2, pp. 208–213, 2009.

[154] P. Anagnostis, M. Florentin, S. Livadas, I. Lambrinoudaki, and D. G. Goulis, "Bone health in patients with dyslipidemias: an underestimated aspect," *International Journal of Molecular Sciences*, vol. 23, no. 3, p. 1639, 2022.

[155] F. Xiao, P. Peng, S. Gao, T. Lin, W. Fang, and W. He, "Inverse association between low-density lipoprotein cholesterol and bone mineral density in young- and middle-aged people: the NHANES 2011-2018," *Frontiers of Medicine*, vol. 9, Article ID 929709, 2022.

[156] W. Fang, P. Peng, F. Xiao, W. He, Q. Wei, and M. He, "A negative association between total cholesterol and bone mineral density in US adult women," *Frontiers in Nutrition*, vol. 9, Article ID 937352, 2022.

[157] L. Cao, W. Wu, X. Deng, H. Guo, F. Pu, and Z. Shao, "Association between total cholesterol and total bone mineral density in US adults: national Health and Nutrition Examination Survey (NHANES), 2011-2018," *Journal of Orthopaedic Surgery and Research*, vol. 18, no. 1, p. 40, 2023.

[158] S. Hu, S. Wang, W. Zhang et al., "Associations between serum total cholesterol level and bone mineral density in older adults," *Aging (Albany NY)*, vol. 15, no. 5, pp. 1330–1342, 2023.

[159] R. Xie, X. Huang, Q. Liu, and M. Liu, "Positive association between high-density lipoprotein cholesterol and bone mineral density in U.S. adults: the NHANES 2011-2018," *Journal of Orthopaedic Surgery and Research*, vol. 17, no. 1, p. 92, 2022.

[160] H. Chen, Z. Shao, Y. Gao, X. Yu, S. Huang, and P. Zeng, "Are blood lipids risk factors for fracture? Integrative evidence from instrumental variable causal inference and mediation analysis using genetic data," *Bone*, vol. 131, Article ID 115174, 2020.

[161] J. Zheng, M. J. Brion, J. P. Kemp et al., "The effect of plasma lipids and lipid-lowering interventions on bone mineral density: a mendelian randomization study," *Journal of Bone and Mineral Research*, vol. 35, no. 7, pp. 1224–1235, 2020.

[162] Q. Zhang, J. Greenbaum, H. Shen et al., "Detecting causal relationship between metabolic traits and osteoporosis using multivariable Mendelian randomization," *Osteoporosis International*, vol. 32, no. 4, pp. 715–725, 2021.

[163] J. I. Barzilay, P. Buzkova, L. H. Kuller et al., "The association of lipids and lipoproteins with hip fracture risk: the cardiovascular health study," *The American Journal of Medicine*, vol. 135, no. 9, pp. 1101–1108.e1, 2022.

[164] S. M. Hussain, P. R. Ebeling, A. L. Barker, L. J. Beilin, A. M. Tonkin, and J. J. McNeil, "Association of plasma high-density lipoprotein cholesterol level with risk of fractures in healthy older adults," *JAMA Cardiol*, vol. 8, no. 3, pp. 268–272, 2023.

[165] P. Yang, D. Li, X. Li et al., "High-density lipoprotein cholesterol levels is negatively associated with intertrochanter bone mineral density in adults aged 50 years and older," *Frontiers in Endocrinology*, vol. 14, Article ID 1109427, 2023.

[166] R. Zhu, Y. Xu, Z. Wang et al., "Higher serum apolipoprotein B level will reduce the bone mineral density and increase the risk of osteopenia or osteoporosis in adults," *Frontiers in Cell and Developmental Biology*, vol. 10, Article ID 1054365, 2022.

[167] H. C. Blair, E. Kalyvioti, N. I. Papachristou et al., "Apolipoprotein A-1 regulates osteoblast and lipoblast precursor cells in mice," *Laboratory Investigation*, vol. 96, no. 7, pp. 763–772, 2016.

[168] M. Lisnyansky, N. Kapelushnik, A. Ben-Bassat et al., "Reduced activity of geranylgeranyl diphosphate synthase mutant is involved in bisphosphonate-induced atypical fractures," *Molecular Pharmacology*, vol. 94, no. 6, pp. 1391–1400, 2018.

[169] T. An, J. Hao, S. Sun et al., "Efficacy of statins for osteoporosis: a systematic review and meta-analysis," *Osteoporosis International*, vol. 28, no. 1, pp. 47–57, 2017.

[170] H. Ohta, Y. Uemura, T. Sone et al., "Effect of bone resorption inhibitors on serum cholesterol level and fracture risk in osteoporosis: randomized comparative study between minodronic acid and raloxifene," *Calcified Tissue International*, vol. 112, no. 4, pp. 430–439, 2023.

[171] Y. S. Zhang, Y. D. Zheng, Y. Yuan, S. C. Chen, and B. C. Xie, "Effects of anti-diabetic drugs on fracture risk: a systematic review and network meta-analysis," *Frontiers in Endocrinology*, vol. 12, Article ID 735824, 2021.

[172] R. H. Mellen, O. S. Girotto, E. B. Marques et al., "Insights into pathogenesis, nutritional and drug approach in sarcopenia: a systematic review," *Biomedicines*, vol. 11, no. 1, p. 136, 2023.

[173] C. H. Tseng, "Pioglitazone reduces dementia risk in patients with type 2 diabetes mellitus: a retrospective cohort analysis," *Journal of Clinical Medicine*, vol. 7, no. 10, p. 306, 2018.

[174] J. Ha, D. W. Choi, K. J. Kim, K. Y. Kim, C. M. Nam, and E. Kim, "Pioglitazone use and reduced risk of dementia in patients with diabetes mellitus with a history of ischemic stroke," *Neurology*, vol. 100, no. 17, pp. e1799–e1811, 2023.

[175] K. R. Tuttle, F. C. Brosius, M. A. Cavender et al., "SGLT2 inhibition for CKD and cardiovascular disease in type 2 diabetes: report of a scientific workshop sponsored by the national kidney foundation," *American Journal of Kidney Diseases*, vol. 77, no. 1, pp. 94–109, 2021.

[176] A. Shafiq, E. Mahboob, M. A. Samad, M. H. Ur Rehman, and Z. H. Tharwani, "The dual role of empagliflozin: cardio renal protection in T2DM patients," *Annals of medicine and surgery (2012)*, vol. 81, Article ID 104555, 2022.

[177] L. Pistelli, F. Parisi, M. Correale et al., "Gliflozins: from antidiabetic drugs to cornerstone in heart failure therapy-A boost to their utilization and multidisciplinary approach in the management of heart failure," *Journal of Clinical Medicine*, vol. 12, no. 1, p. 379, 2023.

[178] S. Rao, "Use of sodium-glucose cotransporter-2 inhibitors in clinical practice for heart failure prevention and treatment: beyond type 2 diabetes. A narrative review," *Advances in Therapy*, vol. 39, no. 2, pp. 845–861, 2022.

[179] S. I. Taylor, J. E. Blau, and K. I. Rother, "Possible adverse effects of SGLT2 inhibitors on bone," *Lancet Diabetes and Endocrinology*, vol. 3, no. 1, pp. 8–10, 2015.

[180] E. Mannucci and M. Monami, "Bone fractures with sodium-glucose Co-transporter-2 inhibitors: how real is the risk?" *Drug Safety*, vol. 40, no. 2, pp. 115–119, 2017.

[181] K. Jackson and K. F. Moseley, "Diabetes and bone fragility: SGLT2 inhibitor use in the context of renal and cardiovascular benefits," *Current Osteoporosis Reports*, vol. 18, no. 5, pp. 439–448, 2020.

[182] Z. Zhou, M. Jardine, V. Perkovic et al., "Canagliflozin and fracture risk in individuals with type 2 diabetes: results from the CANVAS Program," *Diabetologia*, vol. 62, no. 10, pp. 1854–1867, 2019.

[183] C. Arnott, R. A. Fletcher, and B. Neal, "Sodium glucose cotransporter 2 inhibitors, amputation risk, and fracture risk," *Heart Failure Clinics*, vol. 18, no. 4, pp. 645–654, 2022.

[184] J. Gatwood, M. Chisholm-Burns, R. Davis et al., "Evidence of chronic kidney disease in veterans with incident diabetes mellitus," *PLoS One*, vol. 13, no. 2, Article ID e0192712, 2018.

[185] M. Ketteler, G. A. Block, P. Evenepoel et al., "Executive summary of the 2017 KDIGO chronic kidney disease-mineral and bone disorder (CKD-MBD) guideline update: what's changed and why it matters," *Kidney International*, vol. 92, no. 1, pp. 26–36, 2017.

[186] N. B. Watts, "The fracture risk assessment tool (FRAX®): applications in clinical practice," *Journal of Women's Health*, vol. 20, no. 4, pp. 525–531, 2011.

[187] A. Agarwal, W. D. Leslie, T. V. Nguyen, S. N. Morin, L. M. Lix, and J. A. Eisman, "Predictive performance of the garvan fracture risk calculator: a registry-based cohort study," *Osteoporosis International*, vol. 33, no. 3, pp. 541–548, 2022.

[188] A. Agarwal, W. D. Leslie, T. V. Nguyen, S. N. Morin, L. M. Lix, and J. A. Eisman, "Performance of the garvan fracture risk calculator in individuals with diabetes: a registry-based cohort study," *Calcified Tissue International*, vol. 110, no. 6, pp. 658–665, 2022.

[189] R. H. Whitlock, W. D. Leslie, J. Shaw et al., "The Fracture Risk Assessment Tool (FRAX®) predicts fracture risk in patients with chronic kidney disease," *Kidney International*, vol. 95, no. 2, pp. 447–454, 2019.

[190] S. A. Jamal, S. L. West, and T. L. Nickolas, "The clinical utility of FRAX to discriminate fracture status in men and women with chronic kidney disease," *Osteoporosis International*, vol. 25, no. 1, pp. 71–76, 2014.

[191] K. L. Naylor, A. X. Garg, G. Zou et al., "Comparison of fracture risk prediction among individuals with reduced and normal kidney function," *Clinical Journal of the American Society of Nephrology*, vol. 10, no. 4, pp. 646–653, 2015.

[192] L. C. Desbiens, A. Sidibé, C. Beaudoin, S. Jean, and F. MacWay, "Comparison of fracture prediction tools in individuals without and with early chronic kidney disease: a population-based analysis of CARTaGENE," *Journal of Bone and Mineral Research*, vol. 35, no. 6, pp. 1048–1057, 2020.

[193] J. Przedlacki, J. Buczyńska-Chyl, P. Koźmiński et al., "FRAX prognostic and intervention thresholds in the management of major bone fractures in hemodialysis patients: a two-year prospective multicenter cohort study," *Bone*, vol. 133, Article ID 115188, 2020.

[194] P. Y. Wu, S. C. Chen, Y. C. Lin et al., "Role of fracture risk assessment tool and bone turnover markers in predicting all-cause and cardiovascular mortality in hemodialysis patients," *Frontiers of Medicine*, vol. 9, Article ID 891363, 2022.

[195] K. L. Naylor, W. D. Leslie, A. B. Hodsman, D. N. Rush, and A. X. Garg, "FRAX predicts fracture risk in kidney transplant recipients," *Transplantation*, vol. 97, no. 9, pp. 940–945, 2014.

[196] A. Velioglu, B. Kaya, B. Aykent et al., "Low bone density, vertebral fracture and FRAX score in kidney transplant recipients: a cross-sectional cohort study," *PLoS One*, vol. 16, no. 4, Article ID e0251035, 2021.

[197] F. Zappulo, M. Cappuccilli, A. Cingolani et al., "Vitamin D and the kidney: two players, one console," *International Journal of Molecular Sciences*, vol. 23, no. 16, p. 9135, 2022.

[198] J. Kim, J. Ha, C. Jeong et al., "Bone mineral density and lipid profiles in older adults: a nationwide cross-sectional study," *Osteoporosis International*, vol. 34, no. 1, pp. 119–128, 2023.

[199] J. Lee, E. H. Bae, S. W. Kim et al., "The association between vitamin D deficiency and risk of renal event: results from the Korean cohort study for outcomes in patients with chronic kidney disease (KNOW-CKD)," *Frontiers of Medicine*, vol. 10, Article ID 1017459, 2023.

[200] M. Ghahremani, E. E. Smith, H. Y. Chen, B. Creese, Z. Goodarzi, and Z. Ismail, "Vitamin D supplementation and incident dementia: effects of sex, APOE, and baseline cognitive status," *Alzheimer's and Dementia*, vol. 15, no. 1, Article ID e12404, 2023.

[201] R. Shi, Z. Mei, Z. Zhang, and Z. Zhu, "Effects of statins on relative risk of fractures for older adults: an updated systematic review with meta-analysis," *Journal of the American Medical Directors Association*, vol. 20, no. 12, pp. 1566–1578.e3, 2019.

[202] National Institute for Health and Care Excellence, *Clinical Guidelines. Cardiovascular Disease: Risk Assessment and Reduction, Including Lipid Modification*, National Institute for Health and Care Excellence (NICE) Copyright © NICE 2023, London, UK, 2023.

[203] R. Onaisi, R. Dumont, J. Hasselgard-Rowe, D. Safar, D. M. Haller, and H. Maisonneuve, "Multimorbidity and statin prescription for primary prevention of cardiovascular diseases: a cross-sectional study in general practice in France," *Frontiers of Medicine*, vol. 9, Article ID 1089050, 2022.

[204] S. I. McFarlane, R. Muniyappa, R. Francisco, and J. R. Sowers, "Pleiotropic effects of statins: lipid reduction and beyond," *Journal of Clinical Endocrinology and Metabolism*, vol. 87, no. 4, pp. 1451–1458, 2002.

[205] T. Hara, Y. Hijikata, Y. Matsubara, and N. Watanabe, "Pharmacological interventions versus placebo, no treatment or usual care for osteoporosis in people with chronic kidney disease stages 3-5D," *Cochrane Database of Systematic Reviews*, vol. 7, no. 7, Article ID Cd013424, 2021.

[206] P. Khairallah and T. L. Nickolas, "Effectiveness of pharmacological interventions for treatment of osteoporosis in patients with CKD 3-5D: No clear choices," *American Journal of Kidney Diseases*, vol. 80, no. 6, pp. 797–800, 2022.

[207] D. Cejka, R. Wakolbinger-Habel, E. Zitt et al., "[Diagnosis and treatment of osteoporosis in patients with chronic kidney disease: joint guidelines of the Austrian society for bone and mineral research (ögkm), the Austrian society of physical and rehabilitation medicine (ögpmr) and the Austrian society of Nephrology (ögn)]," *Wiener Medizinische Wochenschrift*, vol. 173, no. 13-14, pp. 299–318, 2023.

[208] A. A. Yusuf, S. R. Cummings, N. B. Watts et al., "Real-world effectiveness of osteoporosis therapies for fracture reduction in post-menopausal women," *Archives of Osteoporosis*, vol. 13, no. 1, p. 33, 2018.

[209] S. Davis, E. Simpson, J. Hamilton et al., "Denosumab, raloxifene, romosozumab and teriparatide to prevent osteoporotic fragility fractures: a systematic review and economic evaluation," *Health Technology Assessment*, vol. 24, no. 29, pp. 1–314, 2020.

[210] T. Kobayakawa, A. Miyazaki, Y. Kanayama et al., "Comparable efficacy of denosumab and romosozumab in patients with rheumatoid arthritis receiving glucocorticoid administration," *Modern Rheumatology*, vol. 33, no. 1, pp. 96–103, 2023.

[211] I. R. Reid and E. O. Billington, "Drug therapy for osteoporosis in older adults," *The Lancet*, vol. 399, no. 10329, pp. 1080–1092, 2022.

[212] A. Bastounis, T. Langley, S. Davis et al., "Assessing the effectiveness of bisphosphonates for the prevention of fragility fractures: an updated systematic review and network meta-analyses," *JBMR Plus*, vol. 6, no. 5, Article ID e10620, 2022.

[213] J. O'Kelly, R. Bartsch, N. Kossack, J. Borchert, M. Pignot, and P. Hadji, "Real-world effectiveness of osteoporosis treatments in Germany," *Archives of Osteoporosis*, vol. 17, no. 1, p. 119, 2022.

[214] C. Ayers, D. Kansagara, B. Lazur, R. Fu, A. Kwon, and C. Harrod, "Effectiveness and safety of treatments to prevent fractures in people with low bone mass or primary osteoporosis: a living systematic review and network meta-analysis for the American college of physicians," *Annals of Internal Medicine*, vol. 176, no. 2, pp. 182–195, 2023.

[215] A. Qaseem, L. A. Hicks, I. Etxeandia-Ikobaltzeta et al., "Pharmacologic treatment of primary osteoporosis or low bone mass to prevent fractures in adults: a living clinical guideline from the American college of physicians," *Annals of Internal Medicine*, vol. 176, no. 2, pp. 224–238, 2023.

[216] J. G. Sfeir and R. J. Pignolo, "Pharmacologic interventions for fracture risk reduction in the oldest old: what is the evidence?" *JBMR Plus*, vol. 5, no. 10, Article ID e10538, 2021.

[217] J. D. Niznik, M. A. Gilliam, C. Colón-Emeric et al., "Controversies in osteoporosis treatment of nursing home residents," *Journal of the American Medical Directors Association*, vol. 23, no. 12, pp. 1928–1934, 2022.

[218] B. A. Cedeno-Veloz, J. Erviti Lopez, M. Gutiérrez-Valencia et al., "Efficacy of antiresorptive treatment in osteoporotic older adults: a systematic review and meta-analysis of randomized clinical trials," *The Journal of Nutrition, Health and Aging*, vol. 26, no. 8, pp. 778–785, 2022.

[219] M. Guillaumin, B. Poirson, A. Gerazime et al., "Fractures reduction with osteoporotic treatments in patients over 75-year-old: a systematic review and meta-analysis," *Frontiers in Aging Series*, vol. 3, Article ID 845886, 2022.

[220] S. R. Cummings, J. S. Martin, M. R. McClung et al., "Denosumab for prevention of fractures in postmenopausal women with osteoporosis," *New England Journal of Medicine*, vol. 361, no. 8, pp. 756–765, 2009.

[221] H. G. Bone, R. B. Wagman, M. L. Brandi et al., "10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension," *Lancet Diabetes and Endocrinology*, vol. 5, no. 7, pp. 513–523, 2017.

[222] S. Nayak and S. L. Greenspan, "Osteoporosis treatment efficacy for men: a systematic review and meta-analysis," *Journal of the American Geriatrics Society*, vol. 65, no. 3, pp. 490–495, 2017.

[223] A. Dong, X. Fei, Y. Huang, and Y. Huang, "Efficacy of anti-osteoporosis treatment for men with osteoporosis: a meta-analysis," *Journal of Bone and Mineral Metabolism*, vol. 41, no. 2, pp. 258–267, 2023.