Chronic Kidney Disease: The Silent Enemy?

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Chronic kidney disease (CKD) has become increasingly prevalent in our aging patient population, especially because glomerular filtration rate (GFR) and renal reserve decline progressively as we grow older.[1] The presence of CKD has important implications for our patients undergoing surgery and anesthesia. These may range from impaired handling of anesthetic agents to multiorgan dysfunction and general debility, and specific problems associated with renal replacement therapy (RRT) and transplantation.

Our ability to evaluate renal function and diagnose CKD is largely dependent on measurement of the serum creatinine (SCr), which reflects the steady-state equilibrium between creatinine production from muscle and creatinine excretion by glomerular filtration.[2] However, the SCr is a poor indicator of acute changes in the GFR because it may take hours to days before abrupt declines in GFR are matched by a commensurate increase in SCr. Even in steady-state situations, the SCr may be a misleading indicator of GFR because SCr may not increase above normal laboratory limits until the GFR declines below 50 mL/min. Thus, a 20-year-old patient, a 60-year-old patient, and an 80-year-old patient may all have an SCr in the normal range even though the average GFR for these age groups is 125 mL/min, 80 mL/min, and 60 mL/min, respectively. In a sense, the creeping decline in renal reserve is a silent enemy, because it is not diagnosed or even appraised by standard laboratory screening of renal function. Indeed, patients with malnutrition or cachexia produce so little creatinine from their depleted muscle mass that their SCr may remain in the normal range even when GFR declines to as low as 30 mL/min.[3]

A more meaningful assessment of renal function and reserve is obtained by an estimation of GFR using clearance techniques (creatinine, inulin), or by measuring plasma decay of isotopic markers. However, these are time consuming, involve a varying degree of complexity, and are themselves subject to error. In steady-state situations, nephrologists have long relied on a simple nomogram such as the Cockcroft–Gault equation to calculate an estimated GFR (eGFR), which is based upon patient gender, age, weight, and SCr.[4] The Cockcroft–Gault equation has subsequently been displaced by the Modification of Diet in Renal Disease (MDRD) nomogram, which is independent of body weight, and is expressed per 1.73 M^2 body surface area[5]:

$$\text{eGFR} = 186 \times (S_{cr})^{-1.154} \times (\text{Age})^{-0.203}$$

The eGFR is modified by a factor of 0.742 for female patients and 1.212 for African-American patients.

Although the MDRD is a convenient and relatively reliable indicator of the severity of CKD, it has some inherent limitations. It is generally accepted that the MDRD provides accurate GFR assessment between 20 and 60 mL/min/1.73 M^2 only. In general, there is so much variability in normal GFR that any eGFR calculated >60 mL/min/1.73 M^2 is referred to as a "normal" GFR. Although it is weighted for age, the MDRD is still largely dependent on the SCr and does not consider acute changes in GFR or depleted muscle mass, as detailed above. Nonetheless, it has become established as the "gold standard" of estimation of GFR in stable patients with CKD.

In 2002 the National Kidney Foundation (NKF) used the MDRD to categorize CKD into 5 stages of increasing severity (Table 1); the criteria must have been present for longer than 3 months.[6,7] Stage 1 CKD includes patients who have a normal eGFR (>90 mL/min/1.73 M^2) but are found to have kidney damage defined by the presence of abnormal markers such as albuminuria. Stage 2 CKD is defined as the presence of kidney damage with an eGFR between 60 and 89 mL/min/1.73 M^2. (Again, from a practical standpoint it should be recognized that any MDRD eGFR >60 mL/min/1.73 M^2 is referred to as a "normal" GFR.) Stages 3 and 4 are characterized by diminishing eGFR, to 30 to 59 and 15 to 29 mL/min/1.73 M^2, respectively. Stage 5 patients have an eGFR <15 mL/min/1.73 M^2 or have become dependent on dialysis.

Some notes on terminology are warranted. RRT encompasses the gamut of dialysis (hemodialysis, peritoneal dialysis, continuous venovenous hemodialysis) as well as renal transplantation. End-stage renal disease is a Medicare-defined term that refers to CKD treated with RRT; it is not applied to stage 4 or 5 CKD patients not receiving these treatments.

Using the above definitions, it has been estimated that almost 20 million individuals (about 7% of the population) in the United States suffer from CKD.[8] Of these, about 7.5

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Table 1. Stages of CKD (National Kidney Foundation Kidney Disease Outcomes Quality Initiative Classification)

CKD stage	eGFR mL/min/1.73 M^2	Description
1	>90	Kidney damage with normal GFR
2	60–89	Kidney damage with mildly decreased GFR
3	30–59	Moderately decreased GFR
4	15–29	Severely decreased GFR
5	<15 or RRT	Kidney failure

CKD = chronic kidney disease; eGFR is estimated glomerular filtration rate calculated by the Modification of Diet in Renal Disease (MDRD) nomogram; RRT = renal replacement therapy.

million have stage 3 CKD, and about three-quarters of a million have stages 4 and 5 CKD.

What are the implications? There is substantial evidence that preexisting CKD increases perioperative risk.[9] Most of the data have been obtained in patients undergoing major surgery, notably high-risk vascular surgery or cardiac surgery with cardiopulmonary bypass. For example, in a large study on 37,735 patients undergoing coronary artery bypass graft surgery, Yeo et al. found that operative mortality increased exponentially with increasing stages of CKD.[10] In comparison with patients who had an eGFR >60 mL/min/1.73 M^2, mortality was increased by 18%, 223%, and 439% in patients with stages 3, 4, and 5 CKD, respectively.

In this edition of *Anesthesia & Analgesia*, Ackland et al.[11] have used the MDRD equation to calculate preoperative eGFR in 526 patients aged 50 years or older undergoing elective major joint replacement procedures. They observed postoperative morbidity prospectively using a validated survey, the Postoperative Morbidity Survey (POMS).[12] In comparison with patients with preoperative eGFR ≥60 mL/min/1.73 M^2, patients with eGFR ≤50 mL/min/1.73/M^2, which comprised more than one quarter of their population, had significantly increased postoperative pain and morbidity, and longer recovery times and hospital length of stay. Significant postoperative morbidity involved the pulmonary, cardiovascular, renal, and nervous systems as well as postoperative sepsis.

Given the relatively large literature on the impact of CKD on postoperative morbidity and mortality that already exists,[9] what new information does the Ackland et al. study provide us? First, it addresses an orthopedic surgical population in which the connection between preexisting CKD and postoperative morbidity has not previously been characterized. It does this prospectively using a validated tool (the POMS) that provides us with a means of evaluating the risk of CKD in a wide variety of other noncardiac surgical procedures. Second, it increases our awareness that as our surgical population ages, we should expect a higher incidence of CKD. It is noteworthy that in the Ackland et al. study, the mean age of patients with eGFR ≥60 mL/min/1.73 M^2 was 66 years, in comparison with a mean age of 74 years in patients with eGFR ≤60 mL/min/1.73 M^2.

The Ackland et al. study adds measurably to our understanding of the perioperative risk of CKD, but it does have one unfortunate limitation. Instead of using the NKF stages of CKD as outlined in Table 1 (an eGFR of 30 to 59, 15 to 29, and <15 mL/min/1.73 M^2 for stages 3, 4, and 5 CKD), the authors chose to divide their population into subgroups on the basis of an eGFR of 50 to 59, 40 to 49, and 20 to 39 mL/min/1.73 M^2, and excluded patients with eGFR <20 mL/min/1.73 M^2 or those on dialysis. Thus, one cannot draw conclusions from their study that directly relate to the NKF stage of CKD. In fact, the authors found a "cut-off" eGFR of <50 mL/min/1.73 M^2, below which morbidity and mortality increased considerably. Patients with an eGFR of 50 to 59 mL/min/1.73 M^2 had morbidity and mortality that differed little from patients with "normal" eGFR >60 mL/min/1.73 M^2. Although the study was likely underpowered to detect differences in outcome among stages 3, 4, and 5 CKD, this would be useful information. Nonetheless, it does alert us to the significantly increased risk represented by an eGFR <50 mL/min/1.73 M^2 in this population.

Notably, this study cannot begin to address the question of why patients with CKD have such an increased morbidity or mortality. It is clear that CKD must be considered a multisystem disease and that no organ system emerges unscathed. What is the common factor? It is very unlikely that it is urea itself. We know that although RRT controls very well the acute manifestations of uremia (hyperkalemia, acidosis, fluid overload, encephalopathy, enteropathy, and serositis), many others—such as anemia, thrombocytopathy, osteodystrophy, delayed wound healing, and increased susceptibility to sepsis—are incompletely controlled, if at all. We are beginning to understand that there is a multiplicity of unmeasured toxins besides urea that accumulate in CKD and that may play a role in organ dysfunction. More than 90 such toxins have already been identified,[13] and include compounds such as β_2-microglobulin, advanced glycation end products, advanced oxidation protein products, granulocyte inhibitory proteins, and homocysteine, among others.[14] It is understood that small molecules (<500 Da) that are not protein bound, and which include urea and creatinine, are very easily dialyzed by all forms of RRT.[15] However, larger, so-called "middle molecules" (>500 Da), or those that are protein bound, are poorly cleared by dialysis. These include inflammatory cytokines such as interleukins, tumor necrosis factor, and complement. Could a low-grade chronic inflammatory state exist in CKD that predisposes patients to multiorgan morbidity after major surgery? In patients with CKD who are not dialysis dependent, it is likely that these toxins accumulate *pari passu* with diminishing GFR, which may account for the exponential relationship of postoperative morbidity to advancing stages of CKD. For example, a small molecule, asymmetric dimethylarginine (ADMA), accumulates in patients with CKD well before they require RRT. ADMA inhibits nitric oxide synthase and appears to contribute to arterial stiffness, which is characteristic of vascular comorbidity in patients with CKD.[13,16] Clearly, this is an avenue that bears fruitful ongoing exploration.

Meanwhile, the Ackland et al. study provides a practical, take-home message that is pertinent to all anesthesiologists in clinical practice. We should assess postoperative risk in patients with elevated SCr or advanced age by utilizing the MDRD nomogram to define the CKD stage.

This can be readily accessed on the Internet on the Website of the National Kidney Disease Education Program at http://www.nkdep.nih.gov. All one has to do is insert the patient's age and SCr and the eGFR will be calculated, which allows CKD stage classification. Although some have cautioned against untargeted screening for CKD in the general population,[17] and risk may vary with the nature of the surgical procedure, in this author's opinion this simple and rapid assessment of perioperative risk should be incorporated into routine preoperative anesthetic assessment. And we need more studies like those of Ackland et al. to further define outcomes in all realms of surgery.

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Chronic Kidney Disease and Postoperative Morbidity After Elective Orthopedic Surgery

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BACKGROUND: Reduced estimated glomerular filtration rate (eGFR) is strongly associated with increased cardiovascular risk and all-cause mortality. Associations with morbidity in elective, moderate-risk noncardiac surgery have not been explored. We hypothesized that chronic kidney disease (CKD) would be associated with excess morbidity after elective, moderate-risk orthopedic surgery.

METHODS: Patients undergoing elective orthopedic joint replacement procedures were studied, representing a large proportion of global surgical procedures and characterized by highly homogeneous anesthetic and surgical practice. eGFR was calculated from routine creatinine measurements using the Modification of Diet in Renal Disease equation. CKD was defined as eGFR <60 mL/min/1.73 m^2. Cardiac risk (Revised Cardiac Risk Index) and evidence-based, perioperative factors associated with perioperative morbidity (operative time, blood loss, perioperative temperature) were also recorded prospectively. The primary end point was postoperative morbidity, recorded prospectively using the postoperative morbidity survey. Morbidity differences were analyzed between patients with CKD and normal preoperative renal function (χ^2 test for trend) and presented as hazard ratio (HR) or odds ratio (OR) with 95% confidence intervals (95% CIs). The secondary end points were time to hospital discharge and time to become morbidity free (analyzed by log-rank test), both between and within CKD compared with normal renal function patients. Multiple regression analysis was performed to assess the association of CKD, perioperative factors with morbidity, and length of hospital stay.

RESULTS: Postoperative morbidity survey was recorded in 526 patients undergoing elective orthopedic surgery. CKD patients ($n = 142$; 27%) sustained excess morbidity on postoperative day 5 (OR 2.1 [95% CI: 1.2–3.7]; $P < 0.0001$). CKD patients took longer (HR 1.6 [95% CI: 1.2–1.9]) to become morbidity free (log-rank test, $P < 0.0001$). Time to hospital discharge was delayed by 4 days in CKD patients (HR 1.4 [95% CI: 1.2–1.7]; $P = 0.0001$; log-rank test). CKD patients sustained more pulmonary (OR 2.2 [95% CI:1.3–3.6]; $P = 0.002$), infectious (OR 1.7 [95% CI:1.1–2.7]; $P = 0.01$), cardiovascular (OR 2.4 [95% CI: 1.2–4.8]; $P = 0.01$), renal (OR 2.3 [95% CI:1.5–3.5]; $P <$ 0.00,001), neurological (OR 4.3 [95% CI:1.3–17.7]; $P = 0.005$), and pain (OR 1.8 [95% CI:1.03–3.1]; $P = 0.04$) morbidities. Further stratification of CKD revealed preoperative eGFR ≤50 mL/min/1.73 m^2 to be associated with more frequent morbidity and longer hospital stay, independent of age. Multiple regression analysis identified CKD ($P = 0.006$) and congestive cardiac failure ($P = 0.002$) as preoperative factors associated with prolonged hospital stay.

CONCLUSIONS: A substantial minority of patients with CKD undergoing elective orthopedic procedures are at increased risk of prolonged morbidity and hospital stay. Preoperative eGFR may enhance perioperative risk stratification beyond traditional risk factors. (Anesth Analg 2011;112:1375–81)

Chronic kidney disease (CKD) affects 5% of the population, including patients dependent on dialysis.[1] CKD, defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, is predictive of increased all-cause[2–8] and cardiovascular mortality in individuals with vascular disease[2,3] and asymptomatic middle-aged individuals.[4,5] CKD integrates several key pathophysiologic etiologies that may contribute to postoperative morbidity/mortality,[6] including increased levels of inflammatory factors,[7] elevated plasma homocysteine,[8] enhanced coagulability,[9,10] excess arterial calcification,[11] and endothelial dysfunction.[12] Meta-analysis of elective, noncardiac (largely vascular) surgical studies shows that CKD is an independent risk factor for postoperative death and cardiovascular events.[12] However, the relationship of chronic, mild renal dysfunction with postoperative morbidity is unclear, particularly in apparently lower-risk patients undergoing moderate-risk surgery. Because the detrimental impact of postoperative morbidity on longer-term outcomes (including mortality) is now well established,[13] assessing the relationship of impaired renal function with postoperative morbidity may be particularly instructive. In the cardiac surgical setting, the eGFR is of value in predicting mortality in patients undergoing cardiac surgery.[14,15]

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Major joint replacement surgery is also associated with perioperative morbidity, particularly in an increasingly elderly population with significant comorbidities.[16–18] We hypothesized that CKD would be associated with excess postoperative morbidity and prolonged hospital stay after elective, moderate-risk orthopedic procedures.

METHODS

Supplementary Table 1 (see Supplemental Digital Content 1, http://links.lww.com/AA/A164) details compliance with the STROBE checklist[19] of items recommended for the reporting of observational studies.

Patient Population

In accordance with local Research Ethical Committee approval and the Ethical Principles for Medical Research Involving Human Subjects as outlined in the Declaration of Helsinki, written informed consent was obtained preoperatively from patients presenting for elective major joint (knee and hip) replacement, including revision procedures, aged 50 years and older, between March 2004 and April 2005 at University College London Hospital, United Kingdom.

Perioperative Care

Surgery and anesthesia were conducted by attending staff. Anesthesia, standardized antibiotic prophylaxis, fluid therapy and physiotherapy care were delivered according to usual local standard of care. Epidural anesthesia/analgesia was discontinued within 36 hours postoperatively to enable mobilization and physiotherapy. Morphine patient-controlled analgesia was administered to patients who had undergone procedures under spinal anesthesia. An acute pain service was available for consultation. Oral fluid and solid intake was encouraged to be resumed on postoperative day 1.

Definition of Renal Function and Perioperative Risk Factors

Preoperative creatinine levels were obtained from routine preoperative blood tests. Glomerular filtration rate (GFR) was estimated from the Modification of Diet in Renal Disease equation[20,21]:

$$\text{eGFR (mL/min/1.73 m}^2) = 186.3 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203}$$

The product of this equation was multiplied by a correction factor of 0.742 for women and 1.212 for African American subjects. CKD was defined as eGFR <60 mL/min per 1.73 m^2, according to the Kidney Disease Outcomes Quality Initiative classification.[22] CKD patients were further categorized a priori into 3 subgroups depending on their eGFR: 59 to 50, 49 to 40, or 39 to 20 mL/min/1.73 m^2, according to recent population-based studies exploring long-term cardiovascular risk.[8] Patients requiring dialysis and those with eGFR ≤20 mL/min/1.73 m^2 were excluded from the study. The Revised Cardiac Risk Index was used to assess cardiac risk.[23] Evidence-based, perioperative factors associated with perioperative morbidity operative time,[24] blood loss/postoperative hematocrit,[25] and immediate postoperative temperature,[26,27] were collected prospectively.

Table 1. Definitions of Postoperative Morbidity Recorded According to the Postoperative Morbidity Survey

Pulmonary	Has the patient developed a new requirement for oxygen or respiratory support?
Infectious	Is patient currently receiving antibiotics and/or has the patient had a temperature of ≥38°C in the last 24 h?
Renal	Does the patient have any of the following: Oliguria (<500 mL/d)? Creatinine (>30% from preoperative level)? Urinary catheter in situ?
Gastrointestinal	Unable to tolerate enteral diet (oral or tube feed)? Is the patient experiencing nausea, vomiting, or abdominal distention?
Cardiovascular	Has the patient undergone diagnostic tests or therapy within the last 24 h for any of the following: New myocardial infarction? Ischemia or hypotension (requiring drug therapy or fluid therapy >200 mL/h)? Atrial or ventricular arrhythmias? Cardiogenic pulmonary edema/new anticoagulation (warfarin/heparin/Fragmin)?
Neurological	Does the patient have new confusion/delirium, focal deficit, or coma?
Wound complications	Has the patient experienced wound dehiscence requiring surgical exploration or drainage of purulence from the operative wound with/without isolation of organisms?
Hematological	Has the patient required any of the following within the last 24 hours: red blood cells, platelets, fresh frozen plasma, cryoprecipitate?
Pain	Has the patient experienced surgical wound pain significant enough to require parenteral opioids or regional analgesia?

Outcome Measures

Postoperative morbidity survey (POMS) was recorded (Table 1) using a validated system.[16,18] The POMS was administered by 1 of 2 study nurses to consenting patients on postoperative days 3, 5, 8, and 15. The study nurses were blinded to eGFR data. All data and Revised Cardiac Risk Index analyses were conducted independently of data collectors. POMS criteria were evaluated through direct patient questioning and examination, review of clinical notes and charts, retrieval of data from the hospital clinical information system, and/or consulting with the patient's caregivers. Patients were cared for by the normal attending clinicians who were blinded to the survey results. We also recorded patient's age, gender, measures of preoperative risk, ASA physical status score,[28] Physiologic and Operative Severity Score for the enUmeration of Mortality and Morbidity,[29] length of hospital stay, and mortality.

Statistical Analysis

Categorical data are summarized as absolute values (percentage). Continuous data are presented as mean ± SD. Characteristics of patients in different eGFR groups were compared using the χ^2 test for trend, analysis of variance (depending on the distribution and nature of the data), odds ratio, and hazard ratio (HR). Statistical analyses (NCSS 2004; NCSS, Kaysville, UT) of time to discharge

Table 2. Preoperative and Perioperative Characteristics According to Presence of Chronic Kidney Disease

	Normal	Chronic kidney disease	*P* value
Number (%)	383 (73%)	143 (27%)	
Age (y)	66 (65–68)	74 (73–76)	<0.0001
Male, *n* (%)	165 (43%)	15 (23%)	<0.0001
Creatinine (μmol/L)	72 (71–74)	106 (102–110)	<0.0001
ASA grade ≥III, *n* (%)	59 (16%)	37 (26%)	0.01
Revised Cardiac Risk Index ≥2, *n* (%)	177 (47%)	100 (70%)	<0.0001
Diabetes mellitus, *n* (%)	50 (13%)	19 (13%)	
Hypertension, *n* (%)	27 (7%)	14 (10%)	
Cardiac disease, *n* (%)	31(8%)	14 (10%)	
Morbidity predicted by POSSUM (% patients)	21% (19%–22%)	20% (18%–22%)	0.71
White cell count (preoperative) ($\times 10^9$ cells/L)	7.1 (6.9–7.3)	7.4 (6.1–8.6)	0.71
Hip replacement (%)	43%	43%	0.66
Operative time (min)	152 (147–156)	146 (140–152)	0.49
Analgesia			
General anesthesia	35 (9%)	14 (10%)	
General anesthesia	46 (12%)	18 (13%)	0.81
+Neuraxial	57 (15%)	16 (11%)	
Neuraxial alone	245 (64%)	95 (66%)	
General anesthesia + peripheral block			
Postoperative temperature (°C)	36.1 (36.0–36.2)	36.1 (35.9–36.2)	0.89
Preoperative hematocrit	0.40 (0.39–0.41)	0.41 (0.39–0.42)	0.59
Perioperative blood loss (change in hematocrit)	0.08 (0.07–0.09)	0.08 (0.06–0.10)	0.68
Postoperative hematocrit	0.32 (0.31–0.33)	0.33 (0.31–0.34)	0.97

POSSUM = Physiologic and Operative Severity Score for the enUmeration of Mortality and Morbidity.

from hospital and time to presence of no morbidity were performed using Kaplan-Meier survival plots (log-rank test). A hierarchical, forward 1-way switching multiple regression analysis model (NCSS 2004) of numeric and categorical variables was performed to assess the association between preoperative (age, gender, ASA grade, Physiologic and Operative Severity Score for the enUmeration of Mortality and Morbidity score, diabetes, hypertension, previous myocardial infarction, angina, heart failure, preoperative white cell count and hematocrit, absolute eGFR) and other evidence-based perioperative factors (length of operation, postoperative hematocrit and temperature) with length of hospital stay. $P < 0.05$ was considered significant.

Power Calculation

The study was powered on the basis of previous studies demonstrating ≥1.5 times increase in risk of all-cause morbidity in CKD patients.[1–10] Previous noncardiac surgery studies of morbidity demonstrate approximately 50% of patients to have ≥1 postoperative morbidities after similar orthopedic procedures on postoperative day 5.[20,21] From these previous studies, our primary hypothesis was that the absolute incidence of morbidity in those patients with CKD would be >15% higher. Because population data suggested that patients with CKD should constitute approximately 20% of our surgical population,[1–10] group sample sizes of at least 389 (eGFR ≥60 mL/min/1.73 m^2) and 98 (eGFR ≤60 mL/min/1.73 m^2) were required to achieve 80% power to detect a difference between the group proportions of 0.15.[30] The test statistic used was the 2-sided Fisher exact test, with the significance level of the test targeted at <0.05.

RESULTS

Patient Population

Patients with normal renal function were more prevalent, younger ($P < 0.0001$), more likely to be male ($P = 0.001$), and at less perioperative cardiac risk ($P < 0.0001$) as defined by the Revised Cardiac Risk Index (Table 2). Perioperative management, including the use of regional analgesia, postoperative core temperature, and intraoperative blood loss (postoperative change in hematocrit) were also similar between groups.

Table 3. Perioperative Morbidity

	Normal	Chronic kidney disease	*P* value
Pulmonary	48 (13%)	33 (23%)	0.002
Infectious	97 (25%)	53 (37%)	0.01
Cardiovascular	22 (6%)	18 (13%)	0.01
Gastrointestinal	65 (17%)	33 (23%)	0.10
Wound	39 (10%)	22 (15%)	0.09
Renal	103 (27%)	64 (45%)	<0.0001
Neurological	5 (1%)	8 (6%)	0.005
Pain	37 (10%)	22 (15%))	0.04

eGFR and Postoperative Morbidity

Postoperative morbidity occurred more frequently in CKD patients (odds ratio 2.1; 95% confidence intervals [CIs]: 1.2–3.7); $P < 0.0001$; Table 3) throughout the postoperative period (Fig. 1A). CKD was associated with prolonged morbidity (Fig. 1B), as defined by the time required to become morbidity free postoperatively (HR 1.6 [95% CI: 1.2–1.9]; $P < 0.0001$; log-rank test). Specific patterns of morbidity (Fig. 2A) persisted throughout the postoperative period (Fig. 2B). Within the CKD patient cohort, preoperative eGFR ≤50 mL/min/1.73 m^2 was associated with more morbidity (Supplementary Figs. 1 [see Supplementary Digital Content 2, http://links.lww.com/AA/A165] and 2 [see Supplementary Digital Content 3, http://links.lww.com/AA/A166], see Appendix for supplementary figure legends; Supplementary Table 2 [see Supplementary Digital Content 4, http://links.lww.com/AA/A167]).

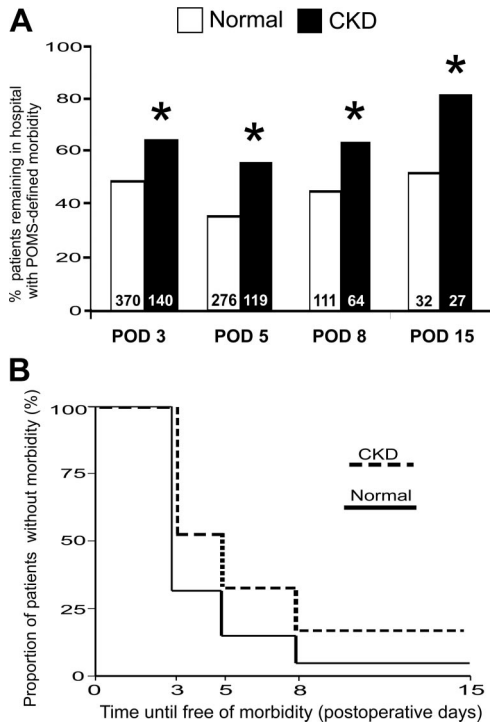

Figure 1. Preoperative estimated glomerular filtration rate (eGFR) and development of postoperative morbidity. A, Total number of postoperative complications according to preoperative eGFR. *$P < 0.01$ compared with eGFR >60 mL/min/1.73 m^2 group. B, Kaplan-Meier plot depicting time to become free of morbidity postoperatively, according to normal or chronic kidney disease (CKD) preoperative levels of renal function. POMS = postoperative morbidity survey; POD = postoperative day.

CKD and the Impact of Morbidity on Length of Hospital Stay

CKD was associated with delayed discharge from hospital (HR 1.4 [95% CI: 1.2–1.7]; $P = 0.0001$; log rank test; Fig. 3A). Time to discharge was prolonged in all patients who sustained early morbidity on postoperative day 3 (HR 2.4 [95% CI: 1.5–3.6]; $P < 0.0001$). However, early morbidity in CKD conferred increased hospital stay (Fig. 3B) even compared with those patients with normal renal function who also sustained similar early postoperative complications (HR 1.3 [95% CI: 1.1–1.7]; $P = 0.02$). Within the CKD patient cohort, preoperative eGFR <50 mL/min/1.73 m^2 was associated with prolonged hospital stay (Supplementary Fig. 3, see Supplementary Digital Content 5, http://links.lww.com/AA/A168; see Appendix for supplementary figure legend). Multiple regression analysis identified CKD ($P = 0.006$) and congestive cardiac failure ($P = 0.002$) as independent preoperative factors associated with prolonged hospital stay. These 2 factors were not associated with each another ($P = 0.47$).

DISCUSSION

A recent meta-analysis of 31 (mostly retrospective) cohort studies demonstrated that CKD conferred increased risk of postoperative death and cardiovascular events in noncardiac surgical patients compared with those with preserved renal function.[12] Our data add significant additional information to previous studies, and underscore the importance of CKD in determining postoperative outcomes[31] for 4 principal reasons.

First, we have demonstrated that even in moderate-risk surgery, there is a clear relationship between CKD and postoperative morbidity. Large epidemiological studies have shown that perioperative morbidity is associated with dramatic differences in postdischarge life expectancy.[13] Second, we provide data that demonstrate the graded relationship between the stage of CKD and prospectively defined postoperative outcomes. Although meta-regression analysis of 5 retrospective studies exclusively conducted in major vascular surgery revealed a graded relationship between severity of CKD and postoperative death,[12] the need for further prospective studies in other noncardiac, particularly nonvascular surgical patients, was highlighted. Importantly, unlike our study, previous reports have not used either standardized or population-based definitions to define CKD.[22] Third, our data are highly consistent with large-scale, epidemiological studies demonstrating that reductions in GFR, particularly <50 mL/min/1.73 m^2, are strongly associated with increased cardiovascular risk and all-cause mortality.[1–10] Translating these data into the perioperative environment using prospectively gathered, validated outcome measures is an important contribution because it provides proof-of-principle for the use of preoperative eGFR as a tool to explore surgical morbidity in wider populations. Fourth, physicians can readily assess the severity of CKD using eGFR, which contributes a numerical, universal scale that permits a more refined assessment of postoperative risk, rather than dichotomous information provided by the presence or absence of comorbid conditions. Importantly, traditional risk factors (cardiovascular/cardiac disease) were present in a minority of patients even in eGFR categories at highest risk of postoperative morbidity. Refinement of current definitions of CKD may enhance risk-prediction tools for noncardiac surgery. Current guidelines[32] classify a serum creatinine of $\geq 177\ \mu mol\ l^{-1}$ as an intermediate, but not major, risk factor for postoperative death or cardiovascular complications. The development of novel models should integrate grades of CKD given the robust strength of these data from both population- and surgical-based cohort studies.

Strengths and Limitations of the Study

The chief strength of this study is the prospective collection of postoperative morbidity data using a validated tool[18] in a noncardiac surgical population undergoing homogeneous, moderate-risk surgery in whom the impact of chronic renal dysfunction on perioperative outcomes has not undergone prospective, systematic evaluation. We used an internationally adopted classification of CKD[22] to explore the relationship between eGFR and postoperative morbidity, because serum creatinine is regarded as an insensitive indicator of renal function.[33] The limitations of the factors included in the Modification of Diet in Renal Disease equation, including age, have been debated extensively, although importantly the equation remains accurate in the borderline kidney disease range. The chief limitation in the Modification of Diet in Renal Disease study equation is the underestimation at higher levels of GFR, which does not apply to our study because we have focused our

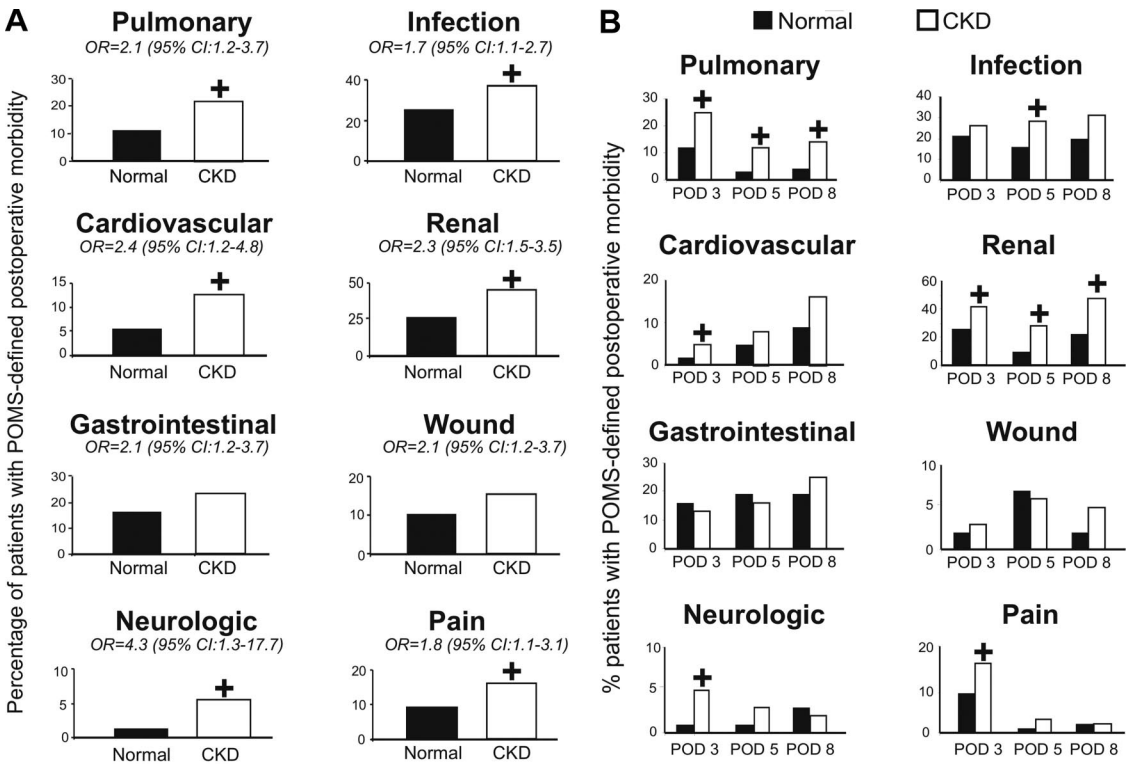

Figure 2. A, Preoperative estimated glomerular filtration rate (eGFR) and specific postoperative morbidities. Number of specific postoperative complications at any point postoperatively according to stratification by preoperative eGFR. *P* values refer to comparisons between normal and chronic kidney disease (CKD) groups; plus sign denotes increased risk (determined by significant odds ratio [OR] [95% confidence intervals]) for developing morbidity ($P < 0.05$) compared with preoperative normal renal function (eGFR >60 mL/min/1.73 m^2). B, Preoperative eGFR and patterns of specific postoperative morbidities over time. Patterns of specific complications on postoperative days (PODs) 3, 5, 8, and 15, according to normal kidneys or CKD defined by preoperative eGFR. *P* values refer to comparisons between normal and CKD groups; asterisk denotes increased risk (determined by significant odds ratio [95% confidence intervals]) for developing morbidity ($P < 0.05$) compared with preoperative normal renal function (eGFR >60 mL/min/1.73 m^2). POMS = postoperative morbidity survey.

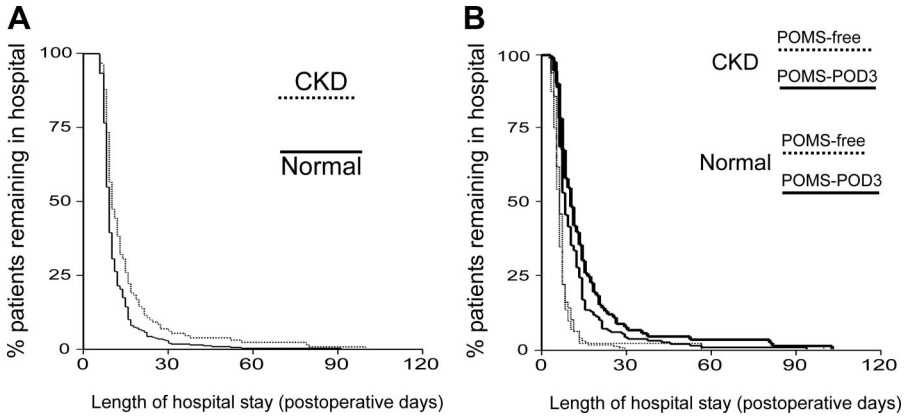

Figure 3. Preoperative estimated glomerular filtration rate (eGFR) and time to hospital discharge. A, Kaplan-Meier plot depicting prolonged time to discharge in patients with chronic kidney disease (CKD), as defined by preoperative eGFR <60 mL/min/1.73 m^2 ($P < 0.0001$; log-rank test). B, Kaplan-Meier plot demonstrating that prolonged time to discharge occurs in CKD patients compared with patients with normal preoperative renal function, independent of sustaining early complications on postoperative day (POD) 3 ($P = 0.02$; log-rank test). POMS = postoperative morbidity survey.

analyses on eGFR <60 mL/min/1.73 m^2. Previous studies have used several definitions for CKD, complicating the interpretation between studies and the clinical application of these results. Our results extend previous work substantially, because we have highlighted the importance of renal dysfunction at levels not deemed to be of clinical significance. Our study was an observational cohort study with the inherent limitations of any observational design. Nevertheless, we have conducted the largest prospectively defined and adequately powered study in a very specific, tightly defined surgical subpopulation to explore the relationship between mild to moderate preoperative renal dysfunction and postoperative outcomes. Our assiduous follow-up and rigorous, prospective definition of postoperative morbidity is an important strength. Furthermore, the previously defined prevalence of postoperative morbidity in this particular surgical population[17,18] guaranteed adequate statistical power to detect associations for a wide range of levels of eGFR. Although hospitalized patients with impaired renal function sustain more adverse safety events,[34] the patterns of morbidity observed in our study were not consistent with such iatrogenic etiologies. For

example, we did not observe any abnormal patterns in perioperative factors between eGFR groups that could contribute to adverse safety, such as postoperative hypothermia[28,35] or differences in pain therapy. Because no intervention was assessed, these data can only provide associative conclusions. We were restricted in our measures of renal function to eGFR. Cystatin C may be a superior predictor of outcomes, particularly in elderly patients.[31] We also have no measure of albuminuria, which may further enhance the predictive value of renal-related pathology.[36]

CONCLUSIONS

Chronic renal disease confers substantially increased risk of postoperative morbidity in homogeneous, elective, moderate-risk orthopedic surgery. Larger studies are required to define the precise contribution that standardized measures of renal function can provide to help refine the stratification of perioperative risk in noncardiac surgery. Preventive perioperative strategies in targeted subpopulations of patients at particularly high risk may be beneficial.

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AUTHOR CONTRIBUTIONS

GLA helped with study design, data analysis, conduct of study, and manuscript preparation; NM and SC helped with data collection; and MPWG and MGM helped with data collection and manuscript preparation.

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APPENDIX: SUPPLEMENTARY FIGURE LEGENDS

Supplementary Figure 1. Time to become free of postoperative morbidity according to severity of chronic kidney disease. Patients with preoperative estimated glomerular filtration rate (eGFR) <50 mL/min/1.73 m^2 experienced slower resolution of morbidity.

Supplementary Figure 2. Severity of chronic kidney disease and specific postoperative morbidities. Number of specific postoperative complications at any point postoperatively according to stratification by preoperative estimated glomerular filtration rate (GFR). Asterisk denotes increased risk (determined by significant odds ratio [95% confidence intervals]) for developing morbidity ($P < 0.05$) compared with preoperative normal renal function.

Supplementary Figure 3. Preoperative estimated glomerular filtration rate (eGFR) and time to hospital discharge. A, Kaplan-Meier plot depicting prolonged time to discharge in patients with preoperative eGFR <50 mL/min/1.73 m^2 ($P < 0.001$). B, Kaplan-Meier plot demonstrating that prolonged time to discharge occurs in chronic kidney disease patients with preoperative eGFR <50 mL/min/1.73 m^2 ($P = 0.01$; log-rank test).

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