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REVIEW

Impact of frailty on perioperative and oncologic outcomes in patients undergoing surgery or ablation for renal cancer: a systematic review

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ABSTRACT

INTRODUCTION: Frailty has been recognized as a major risk factor for adverse perioperative and oncological outcomes in patients with genitourinary malignancies. Yet, the evidence supporting such an association in patients with renal cell carcinoma (RCC) is still sparse. Herein we provide an updated comprehensive overview of the impact of frailty on perioperative and oncologic outcomes in patients undergoing surgery or ablation for RCC.
EVIDENCE ACQUISITION: A systematic review of the English-language literature was conducted using the MEDLINE (*via* PubMed), Web of Science and the Cochrane Library databases according to the principles highlighted by the

EAU Guidelines Office and the PRISMA statement recommendations. The review protocol was registered on PROSPERO (CRD42021242516). The overall quality of evidence was assessed according to GRADE recommendations.
EVIDENCE SYNTHESIS: Overall, 18 studies were included in the qualitative analysis. Most of these were retrospective single-center series including patients undergoing surgery for non-metastatic RCC. The overall quality of evidence was low. A variety of measures were used for frailty assessment, including the Canadian Study of Health and Aging Frailty Index, the five-item frailty index, the Modified Rockwood's Clinical Frailty Scale Score, the Hopkins Frailty score, the Groningen Frailty Index, and the Geriatric nutritional risk index. Sarcopenia was defined based on the Lumbar skeletal muscle mass at cross-sectional imaging, the skeletal muscle index, the total psoas area, or the Psoas Muscle Index. Overall, available studies point to frailty and sarcopenia as potential independent risk factors for worse perioperative and oncological outcomes after surgery or ablation for different RCC stages. Increased patient's frailty was indeed associated with higher risk of perioperative complications, healthcare resources utilization, readmission rates and longer hospitalization periods, as well as potentially lower cancer specific or overall survival.
CONCLUSIONS: Frailty has been consistently associated with worse outcomes after surgery for RCC, reinforcing the value of preoperative frailty assessment in carefully selected patients. Given the low quality of the available evidence (especially in the setting of tumor ablation), prospective studies are needed to standardize frailty assessments and to identify patients who are expected to benefit most from preoperative geriatric evaluation, aiming to optimize decision-making and postoperative outcomes in patients with RCC.

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KEY WORDS: Complications; Frailty; Nephrectomy; Outcomes; Renal Cancer.

Introduction

Frailty is a geriatric syndrome defined as a state of "reduced resilience and increased vulnerability to external stressors", in which even minor events can trigger disproportionate adverse outcomes.[1] Over recent years, frailty is receiving increasing attention in cancer care, in parallel with the aging of the world population.[2] In fact, up to 20% of people aged >65 years are frail and frailty prevalence is known to increase with advancing age.[3, 4] Moreover, while a significant proportion of cancer deaths each year are recorded in older patients, an increasing number of studies have recognized frailty as a major factor impacting oncological, surgical, chemo- and radiotherapeutic outcomes.[2] As such, several clinical practice Guidelines provide recommendations on how to evaluate patient frailty and how to integrate it into the contemporary decision-making schemes for older patients with a variety of oncological diseases.[5-7]

In this scenario, frailty has been object of increasing interest also in the Urological literature. For instance, the most recent European Association of Urology (EAU) Guidelines on prostate cancer dedicated a whole section on the evaluation of patients' health status and life expectancy, and strongly recommended the use of the Geriatric-8 (G8) questionnaire, Mini-COG and Clinical Frailty Scale as tools for health status screening, suggesting referral to comprehensive geriatric assessment for patients with a G8 score <14.[6] The EAU Guidelines on muscle-invasive bladder cancer provided similar recommendations.[8] Recent reports reinforced the importance of frailty assessment in older patients who are candidates for urologic surgery.[9-13]

Unlike other cancers, the evidence supporting an impact of frailty on intra- and postoperative outcomes after surgery for renal cancer is still sparse, despite opinion-leaders and physicians recognize its value for decision-making purposes.[14] As such, the word "frailty" is seldom mentioned by Guidelines.[15-18] and a formal assessment of frailty among older patients with renal cell carcinoma (RCC) is currently not recommended in routine clinical practice.

However, considering the non-negligible proportion of older patients presenting with localized renal masses and their growing life expectancy, especially in Western Countries,[19] assessing the prognostic relevance/role of frailty in RCC surgery is becoming an unmet need from multiple standpoints and for several stakeholders, including clinicians, surgeons, and policy-makers. The incorporation of frailty assessments in clinical decision-making algorithms for patients with localized RCC would ideally allow more tailored treatment strategies, taking into consideration tumor-related features as well as the patient's overall health status.[14] This would ultimately lead to less overtreatment of older patients,[20] efficient use of healthcare resources and prioritization of value-based care.[21]

Herein we provide an updated comprehensive overview of the impact of frailty on perioperative and oncologic outcomes in patients undergoing surgery for RCC.

Evidence acquisition

Review protocol and search strategy

The systematic review was conducted according to the principles highlighted by the EAU Guidelines Office[22] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement recommendations.[23] The review protocol was registered on PROSPERO on March 15th, 2021 (www.crd.york.ac.uk/prospero; registration number: CRD42021242516).

A comprehensive electronic search of the English-language literature was performed combining free-text and Mesh terms using the MEDLINE (Via PubMed), Web of Science and the Cochrane Library databases without time limits. A detailed overview of the literature search strategy is reported in the Supplementary Digital Material 1 (Supplementary Text File 1, Supplementary Table I). To be more inclusive, the term 'sarcopenia' was also added to the search as the concept of impaired muscle mass and function has been previously reported to be one the most important markers and a possible surrogate of frailty.[24, 25] The search was updated on March 24th, 2021 to retrieve additional potential records. A manual search of bibliographies in included studies and previous reviews was also performed to find additional relevant studies. The literature search was performed independently by two authors (R.C. and A.B.).

Inclusion and exclusion criteria

A specific population (P), intervention (I), comparator (C), outcome (O) and study design (S) (PICOS) framework was prespecified to assess the study eligibility, as recommended.[22] The PICOS framework for this review:

- (P): adult patients with metastatic or non-metastatic renal masses, with or without preoperative histological diagnosis of RCC (i.e. at percutaneous renal biopsy), who were candidate for surgery and underwent a comprehensive geriatric/frailty assessment (with any of the available validated instruments) before active treatment;
- (I): partial nephrectomy (PN) or radical nephrectomy (RN) with curative, cytoreductive or palliative intent, or tumor ablation; (C): Comparative or noncomparative series (with at least one study group including patients undergoing surgery or ablation);
- (O): intraoperative and postoperative adverse events, including incident delirium, surgical complications (classified according to the modified Clavien-Dindo classification system), acute kidney injury, transfusion rate, length of hospital stay, 90-d mortality, functional decline; and oncologic outcomes (overall survival [OS)], cancer-specific survival [CSS], recurrence-free survival [RFS]);
- (S): prospective or retrospective studies including at least 10 patients. Studies including only specific patient groups (*i.e.* immunosuppressed patients, transplant recipients, or patients with RCC syndromes) were excluded. In case of multiple articles published by the same group with overlapping patient cohorts, only the study with the largest number of patients was included. Studies with insufficient reporting of the PICOS criteria were excluded.

Study selection and data extraction

The Rayyan Software (https://rayyan.qcri.org/reviews) was used to identify and remove duplicates among included records. Two independent members of the review team (R.C., A.B.) screened the titles and abstracts of the retrieved records using a dedicated screening form according to the PICOS framework for the review. Disagreement was solved by a third party (T.K.). The same authors confirmed study eligibility after full-text screening, following established principles.[22] Separate screening forms were created for each selection phase.

The flow-chart showing the overall review process according to the PRISMA statement is shown in Figure 1.

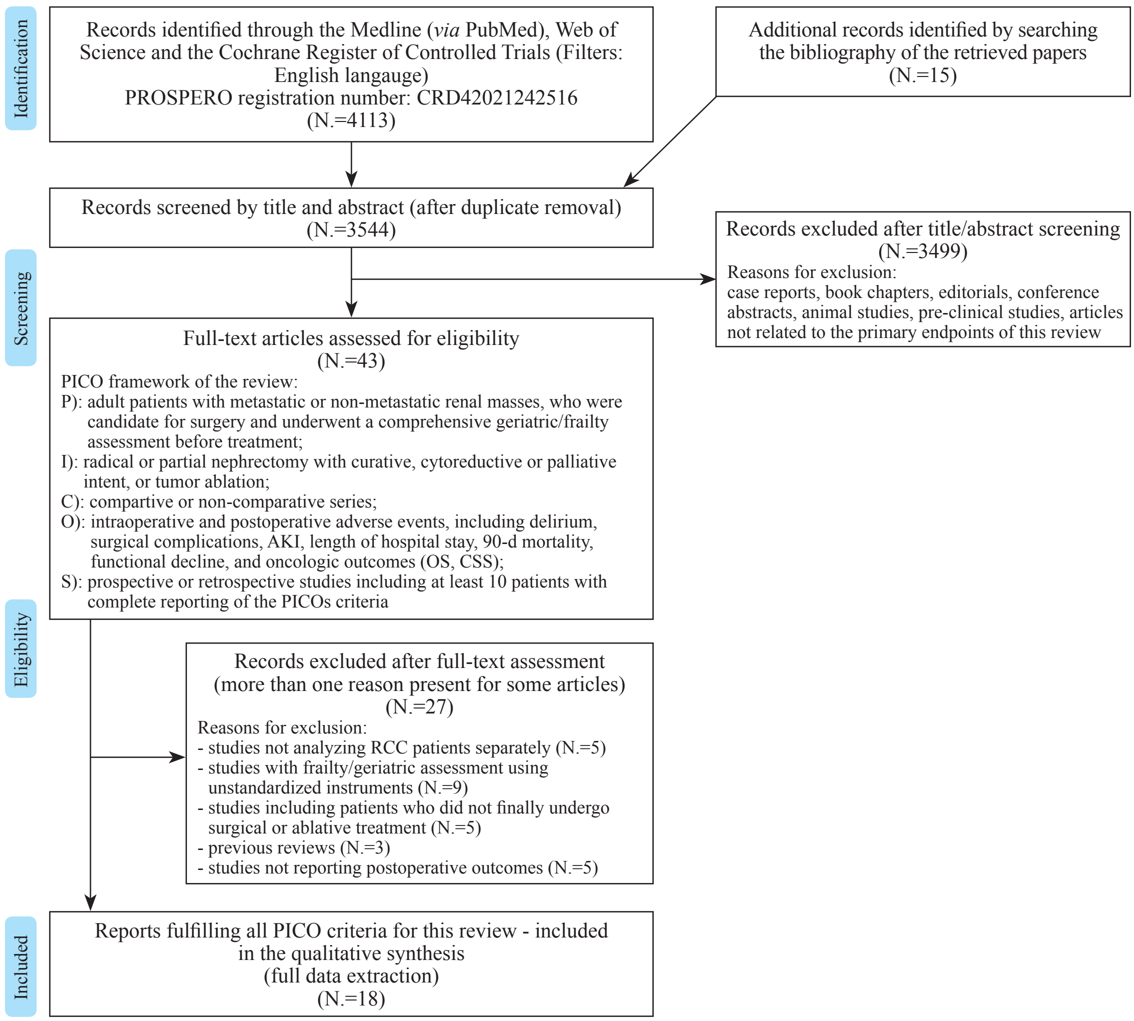


Figure 1.—Flow-chart showing the literature search and systematic review process according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement recommendations.

Data from studies included in the review were extracted in a-priori developed data extraction form by three authors (D.A., A.P., S.E.); then, the reliability and completeness of data extraction was crosschecked by another member of the review team (R.C.). The following information was extracted by each study: study identification (*e.g.* citation; authors; publication year; country; source of data); methods (*e.g.* study design, setting, enrolment period, number of centers); participants characteristics (*e.g.* total number, age, sex, co-morbidity, ethnicity, no. lost to follow-up); frailty assessment (*e.g.* instrument used and mean/median frailty status of the population); disease characteristics (*e.g.* staging, severity, biological behavior, surgical complexity); intervention (*e.g.* surgical technique, intraoperative data, intraoperative adverse events); postoperative outcomes (see above). All discrepancies regarding data extraction were resolved by consensus among the review team members.

Risk of bias in individual studies and synthesis of results

Two reviewers (R.B., O.K.) independently assessed the risk of bias within each individual study according to the Quality In Prognosis Studies (QUIPS) tool.[26] A third reviewer (R.C.)

acted as an arbitrator. The overall quality of evidence was assessed according to Grading of Recommendations Assessment, Development, and Evaluation (GRADE) recommendations (https://www.gradeworkinggroup.org; www.handbook.cochrane.org).

A narrative format was used for the synthesis of qualitative analysis. Owing to the low quality and heterogeneity of the included studies, a quantitative synthesis of the evidence was not pursued.

Evidence synthesis

Study selection

The literature search identified 4128 records; of these, after duplicate removal, 3499 were excluded by title and abstract screening, leaving 45 records for full-text assessment of eligibility. Finally, 18 studies were included in the qualitative analysis of this review.[27-44] Of these, nine were focused on frailty/geriatric assessment,[27-35] two on both frailty and sarcopenia,[37] and seven on sarcopenia.[38-44] The study selection process is summarized in the PRISMA flowchart (Figure 1).

Study characteristics

Overall, most studies included in the review were retrospective single-Centre series and were published after 2015 (Supplementary Digital Material 2: Supplementary Table II).[27-44] Two studies were multicentre,[34, 41] of which one including 4591 patients,[34] while five population-based,[27, 28, 30, 32, 33] enrolling a number of patients ranging between 3644[32] and 37136.[33] The overall quality of evidence according to GRADE was low.

Most studies included patients undergoing surgery (either PN or RN) for non-metastatic RCC. Of note, a few studies included patients undergoing a variety of approaches for locally advanced or metastatic disease (*i.e.* radical nephrectomy plus inferior vena cava thrombectomy;[42] cytoreductive nephrectomy).[32, 38, 40] One study included both patients undergoing surgery and tumor ablation.[35]

RCC-related characteristics were rarely reported in the studies included in this review (Supplementary Digital Material 3: Supplementary Table III).[27-44]

The reporting of the main outcomes included in the PICOS framework of the review was heterogeneous across the included studies (Supplementary Digital Material 4: Supplementary Table IV);[27-44] for instance, intraoperative adverse events were reported by two studies only[32, 40] while postoperative adverse events by seven of 18 (39%) studies. Similarly, only two studies specifically reported the rate of acute kidney injury after surgery/[27, 37] Oncological outcomes (OS, CSS or RFS) were reported by 11 of 18 (61%) studies.[29, 31, 34, 35, 38-44]

A variety of measures were used by different authors to assess frailty and/or to perform the evaluation, including the Canadian Study of Health and Aging Frailty Index (CSHA-FI)[28, 31, 36, 37] or its modifications[27, 32] the five-item Frailty Index (FFI),[33] the Modified Rockwood's Clinical Frailty Scale Score,[35] the Hopkins Frailty score,[36] the Groningen Frailty Index,[36] and the Geriatric nutritional risk index (GNRI).[29, 34]

Sarcopenia was defined based on the Lumbar skeletal muscle mass at cross-sectional imaging[36, 37] (with different cut-offs), the skeletal muscle index (SMI) at computed tomography (CT) scan,[38, 40, 42-44] the total psoas area (TPA),[39] or the psoas muscle index (PMI).[41]

Given the heterogeneity in the definitions of frailty and sarcopenia used by different authors (Table I), the proportions of patients considered as "frail" and/or "sarcopenic" were highly variable among the studies included in the review (Supplementary Table II).

Risk of bias within studies

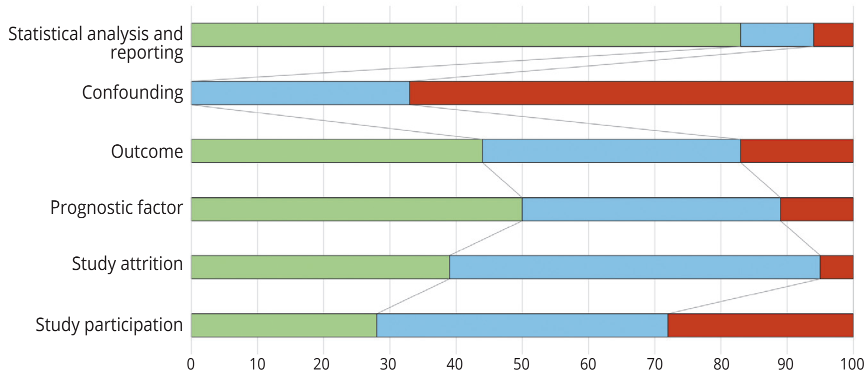
Risk of bias assessment according to the QUIPS tool is shown in Supplementary Digital Material 5 (Supplementary Table V)[27-44] and Figure 2. The proportion of studies with *low risk* of bias in study participation, attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analyses and reporting domains was 27.8%, 38.9%, 50%, 44.4%, 0% and 83.3%, respectively. The domain showing the highest proportion of studies with *high risk* of bias was study confounding (66.7%): this finding can be explained by the retrospective design and

TABLE I.—*Overview of the tools used to define frailty and sarcopenia among the studies included in the review.*

Score	Studies using the score	Variables included in the score
Frailty		
11-variable modified Canadian Study of Health and Aging Frailty Index (11-CSHA)	4	• Functional health status before surgery: partially or totally dependent • Diabetes mellitus type II • Chronic obstructive pulmonary disease • Congestive heart failure • History of myocardial infarction within 6 months • Prior cardiac surgery, percutaneous coronary intervention, or angina within past month • Hypertension • Impaired sensorium • History of transient ischemic attack • History of cerebrovascular accident • Peripheral vascular disease requiring surgery or active claudication present
15-variable Modified-FI (Combination of 11 variables from CHSA and 4 variables for oncologic patients from ACS-NSQIP)	1	• 11-CSHA and: • Weight loss within last 6 months greater than 10% • Chemotherapy or radiation before surgery • History of metastasis • Severe renal failure or currently on dialysis
Five-item frailty index (FFI)	1	• Diabetes • Impaired functional status • Chronic obstructive pulmonary disease • Hypertension requiring medication • Congestive heart failure within 30 d before surgery
Modified Frailty Index (mFI): 10 clusters of frailty-defining diagnoses that comprise the John Hopkins Adjusted clinical groups	1	• Malnutrition • Dementia • Severe vision impairment • Decubitus ulcer • Incontinence of urine • Loss of weight • Fecal incontinence • Social support needs • Difficulty in walking • Fall
Modified Rockwood's Clinical Frailty Scale	1	• 7-point scale based on clinical judgment on whether a patient is fit or frail
Sarcopenia		
Skeletal muscle index (SMI)	7	• Lumbar skeletal muscle mass on CT (computed tomography) or MRI (magnetic resonance imaging) scans
TPA (Total Psoas Area)	1	• Total area of psoas muscle on CT scans
Psoas Muscle Index (PMI)	1	• Psoas muscle area divided by the square of the body height
Nutritional status		
Geriatric Nutritional Risk Index (GNRI)	2	• Albumin, Prealbumin, CRP (C reactive protein) levels • Weight • BMI
Functional status		
Function-related indicators (FRIs)	1	• Reduced functional status (e.g., mobility-assist device, falls, fractures, home oxygen, pressure ulcers) or overlying disability (*e.g.*, dementia, depression, malnutrition, respiratory failure, sepsis)

heterogenous inclusion criteria of most studies included in the review.

In a non-negligible proportion of studies (44.4%, 55.6%, 38.9%, 38.9%, 33.3% and 11.1% for the six domains of the QUIPS tool, respectively), there was a *moderate* risk of bias, often due to lack of reporting key information to enable reliable judgments by the reviewers.



	Study participation	Study attrition	Prognostic factor	Outcome	Confounding	Statistical analysis and reporting
Low risk	28	39	50	44	0	83
Moderate risk	44	56	39	39	33	11
High risk	28	5	11	17	67	6

Figure 2.—Graphical overview of the overall risk of bias and applicability judgements for the fifteen studies included in the review according to the Quality In Prognosis Studies (QUIPS) tool.

Results of individual studies

Studies on frailty

A detailed overview of the results of the six studies assessing the effect of frailty on RCC is shown in Supplementary Table IV.

Walach *et al.*[37] examined the role of frailty and comorbidities in predicting nephron sparing surgery outcomes in 409 patients who underwent PN and 38 who received active surveillance or tumor ablation. Frailty and comorbidities were evaluated using the modified frailty index of the Canadian Study of Health and Aging (11-CSHA) and the age-adjusted Charlson-Comorbidity Index, respectively. Patients undergoing active surveillance or tumor ablation were more likely frail or comorbid compared to those who underwent surgery. Both the 11-CSHA and the age-adjusted Charlson-Comorbidity Index were identified as independent predictors of surgical outcomes. In particular, the 11-CSHA score was an independent predictor of major complications (OR: 3.6, P=0.001) while the age-adjusted Charlson-Comorbidity Index was associated with hospital re-admission (OR: 4.93, P=0.003). Albumin levels and the radiological skeletal-muscle index were also assessed, showing no relevant prognostic value. The main limitation of the study was the retrospective, single-centre design and the lack of granular information on patient's medical therapy.

Lascano *et al.*[27] retrospectively reviewed data from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) registry. The Authors included 41,681 patients treated with prostatectomy, PN or RN, nephroureterectomy or cystectomy. Frailty was assessed using a modified 15-point frailty index. Their results confirmed the independent predictive role of frailty on major surgical complications and 30-day mortality rates. However, this study was flawed by the lack of cancer-specific information, treatment history and longitudinal follow-up after 30 days. Moreover, no information at institutional or surgeon level was available.

Mosquera *et al.*[28] also analyzed data from the ACS-NSQIP, including patients who underwent high-risk elective operative procedures, and confirmed an impact of frailty on postoperative outcomes, with different magnitudes according to the type of procedure. Similar results were reported on the same registry by Taylor *et al.*,[33] who also showed an effect of frailty on health care resource utilization. In particular, the authors revealed an increased risk of health care resource utilization with increasing degrees of patient frailty. Moreover, frailty was associated with a prolonged length of stay and unplanned readmissions as well as with overall and major complications.

Zhang *et al.*[31] analyzed the association of frailty with OS and metastases-free survival in 672 patients with RCC who underwent surgery. The authors analyzed the outcomes of 672 patients, and, after multivariable adjustment, the frailty index was an independent predictor of both OS (HR: 2.43, P=0.002) and metastases-free survival (HR: 2.22, P=0.002). The Authors also proposed two nomograms including frailty to predict OS and metastases-free survival at 3, 5 and 10 years, obtaining an accuracy of approximately 83 and 76%, respectively. The main limitations of their study are the retrospective design and in the lack of information about nutritional status and frailty index in the long-term follow-up.

Lesnyak *et al.*[35] relied on the Rockwood's Clinical Frailty Scale Score and Charlson Comorbidity Index (CCI) to select patients with cT1a kidney tumors for either tumor ablation or enucleoresection. Patients with a higher frailty index were assigned to tumor ablation. They reported the effect of this treatment algorithm on DFS, OS and RFS in 86 patients. and found similar survival rates between treatments with a slight advantage of ablation over resection in terms of DFS (97.4% *vs*. 95.4% at 5 years, P<0.05) and RFS (94.9% *vs*. 93.6% at 5 years, P<0.05). Contrarily, OS was significantly better in the enucleoresection group (74.4% *vs*. 80.9%, P<0.05). In addition, no kidney function deterioration was shown by authors, who concluded that in older patients (>70 years) percutaneous ablation was feasible even in presence of a high frailty burden.

Palumbo *et al.*[32] relied on the National Inpatient Sample to explore the effect of frailty, as defined by the modified frailty index, on complications, failure to rescue and mortality rates after CN. The authors included 3,644 patients treated between 2008 and 2015. Their results showed that frailty was an independent predictor of overall complications but not failure to rescue or in-hospital mortality.

Lastly, Wunderle *et al.*[36] prospectively evaluated the effect of frailty on 150 patients who underwent PN for localized RCC between 2015 and 2018. The authors relied on the Hopkins frailty score and Groningen frailty index showing that patients with a higher score more frequently experience major postoperative complications. Moreover, six measures combined to provide a complete geriatric assessment in a PN score showed to be a significant predictor of major postoperative complication and trifecta failure after multivariable adjustment.

Studies on patient function

A single study was focused on patient function. Using SEER data, Tan *et al.*[30] evaluated the association of function-related indicators with 30-day morbidity, mortality, resource-use, and cost in 19,129 older patients with kidney cancer who underwent non-ablative surgery for localized RCC from 2000–2009. Of 19,129 patients, 5,509 (28.8%) and 3,127 (16.4%) patients with a function-related indicator (FRI) count of 1 and ≥2 were reported, respectively. Most common was the history of fall-related injury, malnutrition, depression, pneumonia, syncope, and mobility-assist device. A higher FRI count was more common among patients who were older, female, unmarried, with lower socioeconomic standing, or a greater comorbidity burden (P<0.001). Cancer stage and surgery type also varied with patient function (P≤0.001). No statistically significant relationship between FRI count and in-hospital covariates was reported. While no difference was reported regarding surgical complications (OR 0.95, 95% CI: 0.86-1.05), patients with ≥2 indicators more often experienced a medical (OR 1.22, 95% CI: 1.10-1.36) or geriatric (OR 1.55, 95% CI: 1.33-1.81) event or died (OR 1.43, 95% CI: 1.10-1.86) within 30 days of surgery compared with patients with no baseline dysfunction. Patients with FRI ≥2 utilized significantly more medical resources and amassed higher acute care expenditures (P<0.001). In terms of cost, the predicted expenditures varied significantly with patient function.

Studies on nutrition

Overall, two studies focused on nutrition were identified. Miyake *et al.*[29] assessed the prognostic value of the Geriatric Nutrition Risk Index (GNRI) in 432 patients with non-metastatic RCC who underwent complete surgical resection (PN or RN). The GNRI was calculated from serum albumin and BMI (GNRI = 1.489 × serum albumin (g/L) + 41.7 × present body weight/ideal body weight) and was found to negatively impact cancer-related survival. Overall, 107 (24.8%) and 325 (75.2%) patients were classified as having normal (GNRI ≤98) and abnormal (GNRI >98) nutritional status, respectively.

Both RFS and CSS were significantly poorer in the low as compared to the high nutritional status group. Moreover, GNRI was independently associated with CSS. The main limitations of this study is the retrospective design and the lack of details regarding OS.

In a multi-center setting, Kang *et al.*[34] investigated the prognostic significance of the GNRI in 4591 consecutive patients with surgically treated clear cell RCC. Preoperative low GNRI was significantly associated with older age, low BMI, diabetes, poor performance status, and presence of symptoms at diagnosis, as well as aggressive tumor characteristics including large tumor size, advanced stage, high nuclear grade, lymphovascular invasion, sarcomatous differentiation, and tumor necrosis. A low GNRI was significantly associated with reduced RFS in localized (pT1-2N0M0) clear cell RCC and with CSS in the entire cohort. Multivariable Cox regression analysis showed that preoperative GNRI (continuous or categorical variable) was an independent predictor of both RFS and CSS.

Studies on sarcopenia

Overall, seven studies evaluated the impact of sarcopenia on patients undergoing RCC surgery.[38-44] In a retrospective single-center study, Sharma *et al.*[38] evaluated the presence of sarcopenia using Skeletal Muscle Index (SMI) calculated on axial images at the third lumbar vertebrae in 93 patients undergoing cytoreductive nephrectomy for metastatic RCC. The study cohort was divided into two groups according to threshold SMI value and BMI (<43 cm^2/m^2 in men with BMI <25 kg/m^2; <53 cm^2/m^2 in men with a BMI >25 kg/m^2, and <41 cm^2/m^2 in women). Overall, 27 patients (29.0%) had sarcopenia before surgery. Sarcopenic patients received neoadjuvant systemic therapy more often than "non-sarcopenic" patients (P=0.022), they had lower BMI (P=0.001), and a higher prevalence of hypoalbuminemia before surgery (P=0.035). Moreover, they more often received blood transfusions (P=0.006), and reported longer length of stay (P=0.02). Median OS was 7 months (95% CI: 0.8-13.2) in sarcopenic patients *versus* 23 months (95% CI: 12.4-33.6) in non-sarcopenic patients. On multivariable analysis, sarcopenia was an independent predictor of OS (HR: 2.13, 95% CI: 1.15-3.92; P=0.016) in addition to number of metastatic sites >2 (HR: 2.09, 95% CI: 1.24-3.53; P=0.006). Main study limitations include the retrospective and single-institution design, as well as the lack of granular details on CSS.

In a retrospective single-center fashion, Fukushima *et al.*[40] analyzed the postoperative outcomes of 37 patients with metastatic RCC who underwent cytoreductive nephrectomy. The authors assessed the SMI, defined as the skeletal muscle areas at the third lumbar vertebra level on computed tomography images taken ≤1 month before and 5 to 6 months after cytoreductive nephrectomy. Stratifying patients into three groups according to the ΔSMI, 12 patients reported ΔSMI ≤-5 (defined as decreased group), 15 patients a ΔSMI of -5 to 5 (stabilized group), and 10 a ΔSMI ≥5 (increased group). Three-year OS rate was 19%, 76%, and 100% for decreased, stabilized and increased groups, respectively (P<0.001). The authors concluded that postoperative changes in the SMI after CN predict OS for patients with mRCC. The main limitations of the study were lack of data about CSS and DFS, as well as retrospective study design and single-center fashion.

Peyton *et al.*[39] investigated the association of sarcopenia with complications and survival in 128 patients undergoing open or laparoscopic RN for advanced (stage III and IV) kidney cancer. In this study, the authors retrospectively evaluated preoperative cross-sectional imaging assessing the total psoas area (TPA) at the level of the third lumbar vertebra. Sarcopenia was defined as TPA related to height (m^2) in the lowest gender-specific quartile. The threshold was defined as <4.271 cm^2/m^2 for men and <3.804 cm2/m2 for women. In the study cohort, 32 (25%) patients had sarcopenia. Mean TPA for men was 5.49 and 4.27 cm^2/m^2 for men and women, respectively (P<0.05). Sarcopenia was associated with risk of major (Clavien-Dindo grade III or higher) complication (P=0.03) and node-positive disease (P=0.01).

Median OS was 55.1 months, and there was no significant increased risk of death in patients with sarcopenia (HR: 1.77, 95% CI: 0.88–4.04). No statistical difference between OS curves was reported even if stratified by gender.

Psutka *et al.*[44] reported the association between severe sarcopenia, and disease progression, as well as CSS and OS in 387 patients with localized RCC who underwent RN. In this series, the authors evaluated baseline lumbar SMI on preoperative computerized tomography, and sarcopenia was defined as SMI less than 55 and 39 cm^2/m^2 for males and females, respectively. Overall, 180 (47%) patients had sarcopenia, and those were older, obese (63% *vs.* 35%, P<0.01, more likely to be male (77% *vs.* 56%, P<0.001), with a smoking history (67% *vs.* 55%, P=0.02), and to have nuclear grade 3 or greater disease (67% *vs.* 60%, P=0.05). Median postoperative follow-up was 7.2 years. Patients with sarcopenia had similar 5-year CSS (79% *vs.* 85%, P=0.05) compared to those without sarcopenia. However, the sarcopenia group reported significantly lower 5-year OS (65% *vs.* 74%, P=0.005). No difference was reported at the Kaplan Meier curves for CSS and disease-free survival at 5-year follow-up. On multivariable analysis, sarcopenia was associated with increased cancer-specific (HR: 1.70, P=0.047) and overall mortality (HR: 1.48, P=0.039).

In a two-center setting, Noguchi *et al.*[41] calculated the normalized Psoas Muscle Index (PMI) in 316 male patients with localized clear cell RCC (ccRCC) who underwent PN or RN. Overall, 158 (50%) reported lower PMI. No difference was reported in 5-year OS according to PMI (P=0.066), while RFS was poorer in the lower PMI group as compared to the "higher PMI" group (P=0.03). Moreover, lower PMI was a significant predictor of 5-year RFS (HR: 2.306, P=0.022). At multivariable analysis, lower PMI (HR: 2.167, P=0.035), tumor size >4 cm (HR: 2.341, P=0.044), and pathological stage>2 (HR:3.660, P<0.001) were independent risk factors for poor RFS. The study lacks details on preoperative features and CSS.

Watanabe *et al.*[42] analyzed the prognostic impact of sarcopenia for patients with RCC and inferior vena cava thrombus undergoing nephrectomy and concomitant thrombectomy. Sarcopenia was assessed using pre-surgical radiographic imaging and determined by sex, BMI, and SMI. Overall, the study population included 83 patients, of these 54 (65%) being sarcopenic. Regarding perioperative outcomes, no difference was reported based on sarcopenia in terms of overall (35.2% *vs.* 27.6%, P=0.482) and major (Clavien-Dindo grade ≥3, 7.4% *vs.* 10.3%, P=0.648) surgical complications rates, as well as median hospitalization time (11 *vs.* 10 days, P=0.148). Patients with sarcopenia showed significantly shorter CSS (P=0.032) and OS (P=0.017). At multivariable analyses, sarcopenia was an independent risk factor for CSS (HR: 2.76, P=0.0212) and OS (HR: 2.93, P=0.014).

In a single-center fashion, Higgins *et al.*[43] retrospectively analyzed the outcomes of 352 patients with localized RCC undergoing PN or RN and calculated individual and combined SMI and the modified Glasgow Prognostic Score (mGPS). Of note, this is the only study measuring SMI *via* either computed tomography or magnetic resonance imaging. Patients met the criteria for sarcopenia by body mass index- and sex-stratified thresholds (SMI lower than 47 and 38 cm^2/m^2 for males and females with a BMI <30 kg/m^2, or SMI lower than 54 and 47 cm^2/m^2 for males and females with a BMI ≥30 kg/m^2, respectively). In the study cohort, 139 (39.5%) patients were classified as sarcopenic at the baseline. The study cohort was stratified into low (nonsarcopenic, low mGPS), medium (sarcopenia only), medium (inflammation only), and high (sarcopenic, high mGPS) risk according to SMI and mGPS. The median follow-up time was 30.4 months. At multivariable analysis, sarcopenia and mGPS were both independently associated with worse OS (HR: 1.64, P=0.006), CSS (HR, 2.01, P=0.009). Risk groups had an increasing association with worse RFS (P=0.015) and CSS (P =0.004) but not OS (P=0.087). The authors analyzed risk groups in comparison with the Stage, Size, Grade, and Necrosis (SSIGN) and the modified International Metastatic RCC Database Consortium (IMDC) score with ROC curves that demonstrated a higher area under the curve for risk groups in comparison with the SSIGN and IMDC scores at 5 years.

Discussion and future perspectives

Frailty is a clinical syndrome characterized by increased vulnerability to external stressors because of age-related decline in reserve and function across multiple physiologic systems.[45] Sarcopenia is defined as an age-related loss of muscle mass and function, which has been considered to represent an indicator of frailty.[46] Importantly, frailty represents a complex, multidimensional interplay between adaptive capacity and resiliency to stressors[2] which is only partly associated with age in cancer patients, being potentially determined or worsened by cancer progression itself.[14] While being challenging to objectify, frailty metrics may outperform the "traditional" surgical risk assessment tools (*i.e.* ASA score, performance status, etc.).[2]

Due to the ongoing demographic shift in the population, the burden of frailty is increasingly impacting healthcare systems and resources around the world,[46] making this topic of significant interest for urologists involved in the care of the ever-growing population of older patients with genitourinary malignancies. In fact, the value of frailty as a potential independent risk factor for adverse outcomes after surgery and as a critical element of decision-making is recognized by opinion-leaders and Guideline panels across several oncological fields.[5-7, 14] Unfortunately, in the field of RCC, the evidence is still relatively scarce and the latest EAU Guidelines did not provide any recommendation on frailty assessment among patients with renal cancer.[47] Of note, while minimally-invasive surgery has been shown to achieve favorable perioperative, functional and oncological outcomes among (carefully selected) elderly patients with renal masses,[48-50] active surveillance and ablative therapies appear particularly appealing in this population given their higher risk of other-cause mortality.[51-53] The current sub-optimal ability to diagnose RCC at the time of decision-making,[54] leading to a non-negligible rate of unnecessary surgeries, further reinforce this concept.

In this scenario, our work provides a comprehensive updated overview of the available evidence on the impact of frailty and sarcopenia on postoperative and oncologic outcomes in patients undergoing surgery for RCC, offering insights on how to standardize and integrate a multidimensional frailty assessment in routine clinical practice.

Despite the heterogeneity and overall low quality of the available evidence, our review clearly highlights that frailty, sarcopenia and nutritional status are associated with worse outcomes across different clinical profiles, including both localized and metastatic RCC. Notably, the International Society of Geriatric Oncology has provided guidance on how to assess frailty and geriatric screening among patients with a variety of genito-urinary malignancies (prostate cancer, bladder cancer and metastatic renal cancer),[55-57] recommending a rapid baseline geriatric screening by means of the G8 questionnaire and the MiniCOG to select those patients who may benefit from a comprehensive geriatric assessment, with the final purpose to identify 3 patient subgroups (fit, pre-frail and frail). Interestingly, while patients considered as "fit" or "vulnerable with reversible conditions" might receive the standard of care treatments, conversely those considered "frail" or "vulnerable without reversible conditions" are suggested to be referred to less invasive treatments. Unfortunately, such recommendations are still not integrated into our current decision-making schemes for patients with localized renal masses or advanced/metastatic RCC yet.[46]

In the present review, frailty was associated with poorer outcomes such as a higher risk of perioperative complications, higher utilization of healthcare resources, longer hospitalization, higher readmission rates as well as potentially poorer CSS and OS (Supplementary Table IV). The studies focusing on sarcopenia, considered an imaging-based "quantitative representation of frailty" (with less heterogeneous definitions across the included series as compared to frailty indexes) (Supplementary Table II), confirmed a potential association with perioperative adverse events[38, 39] and with decreased CSS, yet with conflicting findings regarding OS. These findings suggest that a more detailed knowledge of the influence of frailty on adverse postoperative and oncological outcomes in the short and long term would help clinicians to tailor the treatment strategy according to the patient's specific global health status and frailty level.

The critical importance of frailty in our current decision-making schemes for patients with localized renal masses has been recently reinforced.[14] In particular, frailty may significantly influence treatment choices in older patients with multimorbidity for whom the risk/benefit ratio of active intervention may call for more conservative approaches. While frailty is routinely (yet, subjectively) assessed by clinicians for decision-making purposes, recent studies have shown that a standardized geriatric assessment appears superior to oncologists' judgement for this task in cancer patients.[58]

To improve on value, standardized reporting of frailty and sarcopenia using established, validated metrics would allow to reduce the heterogeneity of current definitions and reach a consensus within the Uro-Oncology community toward a pragmatic, clinically meaningful integration of geriatric assessment in routine multidisciplinary management of RCC patients. Of note, the implementation of screening programs for the identification of frail patients has been associated earlier with reduced surgical mortality.[59]

Our review highlighted a critical lack of evidence on how pre- and postoperative frailty assessments might specifically translate into better outcomes in RCC patients or whether frailty-driven changes in decision-making (*e.g.* surveillance/ablation vs surgery) might improve quality of life. Importantly, it has been shown earlier that frailty is not necessarily irreversible and that multidisciplinary treatment programs (*e.g.* interventions targeting sarcopenia, including nutritional or pharmacological measures) could potentially reverse this syndrome.[46] These findings open new clinical perspectives on the potential modulation of a patient's frailty risk over time and on the possibility to tailor the management strategy for a given renal mass according to the patient's needs and health status.[60]

Lastly, this review highlights a compelling need for high-quality prospective studies evaluating the impact of frailty in patients undergoing surgery or ablation for RCC using standardized metrics.

While the findings of our review cannot be directly transferred into routine clinical decision-making,[14] further research is warranted to shed light on the association between age, comorbidities, and frailty, identifying the best candidates for pre-treatment multidimensional geriatric assessment. Going forward, future studies should also assess the comparative cost-effectiveness of surgery vs ablation vs active surveillance among elderly and/or frailer patients, according to the principles of value-based care.[21]

Such a holistic assessment of patient's health status may allow personalized decision-making, better treatment selection, prevention of postoperative adverse events and ultimately improved oncologic, functional, and quality of life outcomes in patients with RCC.

Limitations of the study

The review findings should be carefully interpreted considering distinct potential limitations at both a review- and study-level. First, although a rigorous methodology was strictly followed to conduct our review, the search strategy may have been still unable to identify all relevant studies assessing the impact of frailty in patients with RCC undergoing surgery or ablation. In addition, we relied only on English-language literature, excluding potentially relevant articles. Furthermore, we did not evaluate the impact of patients' frailty on decision-making regarding the management strategy (*i.e.* active surveillance *versus* surgery *versus* ablation) in patients with localized renal masses.

While our review was intentionally focused on the impact of frailty in patients who are candidates for active treatment, there is currently lack of data on the impact of frailty on functional and oncological outcomes, as well as quality of life, in patients who elect for active surveillance or watchful waiting.[14, 61] In addition, the triggers for delayed interventions[62] among frailer patients who were initially managed with active surveillance are currently unknown.

Notably, at a study-level, the interpretation of our findings is limited to the quantity and quality of the available evidence. Despite a growing interest among clinicians and researchers, the current literature on the impact of frailty on postoperative outcomes in patients with RCC is still sparse and premature, making the overall quality of the evidence low according to GRADE. Most series were indeed retrospective and with moderate to high risk of selection bias, attrition bias, and confounding (Figure 2). In particular, evidence is even more limited as regards patients who are candidate for tumor ablation, or with advanced RCC requiring more invasive treatment strategies. We may suppose that frailty has greater prognostic relevance in these patients and could significantly influence the risk/benefit ratio of treatment and the decision-making process. Indeed, in frailer individuals, life expectancy may be shorter due to competing conditions, which play a more relevant role in patients' prognosis as compared to RCC.

In addition, there was significant heterogeneity in the study design (patient population, outcomes of interest, type of surgical procedure, surgical approach) as well as in the measure tools applied to define frailty and "sarcopenia" (Table I), limiting the potential generalizability of our findings and the comparison of studies included in the review. Although the use of different frailty instruments may allow for detection of different frailty phenotypes, identifying the measure tool that best informs clinical decisions in older candidates for urological surgery is a distinct unmet need. A standardized approach would also be helpful to promote and implement frailty assessment in routine clinical practice.

Future research efforts should thus aim to identify the most appropriate tool to assess frailty in patients who are candidates for RCC surgery, and to evaluate the independent impact of frailty on adverse postoperative and oncological outcomes. Lastly, the relationship between frailty and sarcopenia (used by few authors as a potential marker of frailty) is highly nuanced and should be object of prospective investigations.

Conclusions

In this review we summarized the available evidence on the impact of frailty on postoperative and oncologic outcomes in patients undergoing surgery or ablation for RCC.

Overall, frailty has been consistently associated with worse perioperative outcomes as well as poorer oncological outcomes after surgery across different RCC stages, reinforcing the value of preoperative frailty assessment in carefully selected patients. Yet, the quality of the available evidence is still low, and we found significant heterogeneity across the studies regarding the definition of frailty and the analysis of its potential impact on patients' outcomes, especially in the setting of tumor ablation.

Future endeavors should be focused on standardization of frailty assessment and identification of the best candidates for preoperative geriatric screening and targeted health care interventions, aiming to personalize decision-making, prevent perioperative adverse events and improve oncologic outcomes and quality of life in patients with RCC.

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