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RESEARCH ARTICLE

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Interpreting the risk analysis index of frailty in the context of surgical oncology

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Abstract

Background and Objectives: The Risk Analysis Index (RAI) accurately predicts adverse postoperative outcomes but the inclusion of cancer status in the RAI has raised two key concerns about its suitability for use in surgical oncology: (1) the potential over classification of cancer patients as frail, and (2) the potential overestimation of postoperative mortality for patients with surgically curable cancers.

Methods: We performed a retrospective cohort analysis to assess the RAI's power to appropriately identify frailty and predict postoperative mortality in cancer patients. We assessed discrimination for mortality and calibration across five RAI models—the complete RAI and four variants that removed different cancer-related variables.

Results: We found that the presence of disseminated cancer was a key variable driving the RAI's power to predict postoperative mortality. The model including only this variable [RAI (disseminated cancer)] was similar to the complete RAI in the overall sample ($c = 0.842$ vs. 0.840) and outperformed the complete RAI in the cancer subgroup ($c = 0.736$ vs 0.704, respectively, $p < 0.0001$, Max $R^2 = 19.3\%$ vs. 15.1%, respectively).

Conclusion: The RAI demonstrates somewhat less discrimination when applied exclusively to cancer patients, but remains a strong predictor of postoperative mortality, especially in the setting of disseminated cancer.

KEYWORDS

frailty, postoperative complications, surgical oncology

1 | INTRODUCTION

Surgeons increasingly recognize that frailty is a significant factor in predicting poor postoperative outcomes. Frailty is an age-related syndrome of increased vulnerability to stressors resulting from a multisystem depletion of physiologic reserve.[1] In the perioperative setting, frailty has been shown to predict surgical complications, failure to rescue, mortality, and poor functional outcomes such as loss of independence.[2–5] With rising awareness of frailty's impact on postoperative outcomes, efforts to screen for frailty preoperatively have gained momentum.

The Risk Analysis Index (RAI) was designed to provide an accessible, prospective frailty assessment tool that could be used at the time of clinical visits to inform patient-provider conversations and

perioperative decision making.[6,7] The RAI is a weighted scale based on responses to 14 survey items, integrating information on demographics (i.e., age and sex), comorbidities, cognitive impairment, and physical functioning to generate a score from 0 to 81, with higher scores indicating greater frailty. Prior work has shown that the RAI can be efficiently implemented across multiple hospitals, taking a median 30 s to compute at the point of care and accurately predicting postoperative outcomes.[8,9] In addition to prospective survey assessment, the RAI can also be retrospectively calculated from data in Veterans Affairs (VA) and American College of Surgeons (ACS) Surgical Quality Improvement Programs (SQIPs),[7] accurately predicting adverse Postoperative outcomes, readmission rates and mortality after operations ranging widely in physiologic stress.[10] Prior work using the SQIP-derived RAI scores established a threshold of RAI ≥ 30 to indicate frailty because, across all surgical diagnoses and procedures, it corresponds to the highest risk decile with at least twice the overall rate of mortality and twice the rate of postoperative readmission.[7]

One of the comorbidities that factors into the RAI score is cancer status. Specifically, the prospective RAI survey used to screen for frailty at the point of care asks, "In the past five years, have you been diagnosed with or treated for cancer?" This question is broadly worded to maximize the RAI's sensitivity to capturing patients with any cancer diagnosis, but the inclusion of cancer status in preoperative frailty assessment has raised concerns about the suitability of the RAI for use in surgical oncology settings where the surgical condition being treated is cancer itself. First, there has been concern among surgical oncologists that screening programs using the RAI may overclassify some patients as frail based on the presence of a potentially curable cancer. Cancer status can raise a patient's RAI score by 28–37 points depending on age. Second, there has been concern that the RAI does not adequately capture the unique complexity and diversity of cancer patients to accurately predict postoperative mortality within this cohort. The variation in this population is significant, with patient age, pretreatment health, cancer type and stage playing important roles in patient outcomes. These practical concerns about RAI interpretation and application are increasingly pressing as the RAI is being implemented at a growing number of hospitals across the United States throughout the Veterans Health Administration,[11] and globally through Epic's Clinical Program.[12] To address some of these concerns, we performed a retrospective cohort analysis to assess the RAI's power to accurately identify frailty and predict postoperative mortality in cancer patients. Specifically, we aimed (1) to explore the contribution of cancer status in the RAI's classification of frailty; and (2) assess the RAI's performance across different age strata to better inform clinical interpretation.

2 | MATERIALS AND METHODS

2.1 | Study design

We performed a retrospective cohort analysis of deidentified VASQIP data. The Institutional Review Board at the VA Pittsburgh Healthcare System determined this study to be exempt from review because it utilized pre-existing, deidentified data.

2.2 | Data set

The VASQIP database contains a systematic sample of surgical cases performed within the VA, with each record representing a unique case. Surgical cases are identified based on Current Procedure Terminology (CPT) codes assigned to the case, and trained nurses abstract high-quality, longitudinal variables from the electronic record describing the preoperative, intra-operative and postoperative periods. A detailed description of the inclusion criteria for VASQIP, along with case sampling methods, robustness of the data, and data elements available have been described previously.[13] For this study, we included all noncardiac surgical cases in the VASQIP database from April 1, 2010 to March 31, 2014 for whom vital status of the patient (i.e., alive or deceased) at 1 year postoperatively was available.

2.3 | Variables

2.3.1 | Demographics, cancer status and Postoperative mortality

Demographics included age, sex, race, and ethnicity. Cancer status was defined according to the procedures used in retrospective analysis and validation of the RAI[7] that stipulate that a given VASQIP record is considered to represent a patient with cancer if at least one specific, preoperative cancer-related variable was present in VASQIP (i.e., disseminated cancer, preoperative chemotherapy or preoperative radiation). These are the only preoperative cancer-related variables included in VASQIP's, and as defined, they capture only a subset of patients diagnosed with malignancy. As such, the cancer status defined by these 3 VASQIP variables is likely less sensitive and more specific than the survey version of the RAI, which defines cancer status as any cancer treated in the past 5 years. 180-day postoperative mortality was defined based on vital status and included any record for which the patient died up to 180 days after surgery.

2.3.2 | Surgical procedures

To describe the procedures performed on patients with cancer, we implemented a three-step process to identify the most common families of noncardiac surgical procedures. First, we sorted the subset of cases involving patients with any of the cancer-related variables according to decreasing frequency of CPT, selecting the most frequent CPTs that represented at least 50% of the cohort and grouping the CPTs into mutually exclusive families of procedures. Second, we sorted by CPT code itself to identify and include any less frequent CPT codes that were members of the families identified in Step 1. Finally, after stratifying the cases representing cancer as disseminated or nondisseminated

(e.g., preoperative chemotherapy or radiation), we sorted the cases according to decreasing frequency of procedure family.

2.3.3 | Frailty

We assessed frailty status using five different methods. First, we calculated the complete RAI from VASQIP variables using the method described previously.[7] We then calculated four variants of the RAI by: (1) removing all cancer variables (RAI [without cancer]), (2) including only disseminated cancer (RAI [disseminated cancer]), (3) including only preoperative chemotherapy (RAI [chemotherapy]), and (4) including only preoperative radiotherapy (RAI [radiotherapy]). Consistent with previous work, we used an RAI ≥ 30 to classify patients as frail, applying this dichotomous categorization to all RAI variants.[10]

2.4 | Statistical analysis

After inspecting the data for out of range and missing values, we summarized demographics, cancer-related variables, and postoperative mortality for the entire cohort with descriptive statistics. We also stratified the cohort by whether the patient record included any of the three cancer-related variables to identify the cancer subgroup. To explore the contribution of cancer status in the RAI's classification of frailty, we summarized the proportion of patients in each cohort who classified as frail using each of the five RAI variants. We then fit five univariate logistic regression models with RAI variant as the independent variable and 180-day postoperative mortality as the dependent variable, quantifying model discrimination using c-statistics and model calibration using the Akaike Information Criteria and Maximum R^2 [14,15] and comparing model discrimination using the methods describe by DeLong et al.[16] Finally, to assess the RAI's performance across multiple age strata, we examined the number and proportion of cancer patients within each age strata. We also fit univariate logistic regression models, similar to those described above, to age-specific subgroups of the data. All statistical analysis was carried out using Stata/SE 15.1 (StataCorp LLC). The two-tailed threshold for statistical significance was set to $p < 0.05$.

3 | RESULTS

3.1 | Demographics, cancer-status, and postoperative mortality

The overall cohort contained 480 731 patients with a mean age of 61 years old (SD = 13.1), of whom 92.2% [443 152/480 731] were male and 65.2% [313 470/480 731] were white (see Table 1). Of these patients, 9516 had cancer as indicated by the presence of at least one of the three cancer-related variables: disseminated cancer (66.7% [6344/9516]), chemotherapy treatment (27.8% [2648/9516]) and radiation treatment (25.3% [2408/9516]). The mean age of the cancer subgroup was 65 years old (SD = 10.0) and consisted of 95.3% [9071/9516] male and 66.6% [6336/9516] white patients. Overall, 17 251 (3.6% [17 251/480 731]) of patients died within 180 days of the surgical procedure. The majority of these (n = 14 363) did not have cancer, but consistent with the mortality associated with patients with disseminated malignancy (i.e., 66.7% of our cancer cohort), the 180-day postoperative mortality rate among cancer patients (27.5% [2615/9516]) was more than 8.8 times that of noncancer subgroup (3.1% [14 634/471 215], χ^2 = 1.6e + 04; $p < 0.0001$).

TABLE 1 Demographics and 180-day postoperative mortality of the entire cohort (n = 480 731) and the cancer subgroup (n = 9516).

	Overall cohort		Cancer subgroup	
	n	%	*n*	%
Male sex	443 152	92.2%	9071	95.3%
Race and Ethnicity				
White, not Hispanic	313 470	65.2%	6336	66.6%
White, Hispanic	18 787	3.9%	278	2.9%
Black, not Hispanic	71 625	14.9%	1561	16.4%
Black, Hispanic	1435	0.3%	9	0.1%
American Indian/ Alaskan Native	3570	0.7%	43	0.5%
Asian/Pacific Islander	1741	0.4%	24	0.3%
Unknown	23 265	4.8%	478	5.0%
Missing	46 838	9.7%	787	8.3%
Cancer-related variables				
Preoperative radiation	2408	0.5%	2408	25.3%
Preoperative chemotherapy	2648	0.6%	2648	27.8%
Disseminated cancer	6344	1.3%	6344	66.7%
180-day postoperative mortality	17 251	3.6%	2615	27.5%

Note: Cancer Subgroup defined as those records in the overall cohort containing one or more cancer-related variables.

Abbreviations: *n*, number; %, proportion of cohort.

3.2 | Surgical procedures

Table 2 presents the most frequent surgical procedures within the cancer subgroup, stratified by cases representing disseminated or nondisseminated cancer. Colectomy (and proctectomy) was the most common procedure in both disseminated (10.2% [644/6344]) and nondisseminated cancer (20.5% [649/3172]). Esophagectomy, by contrast, represented 9.2% [291/3172] of procedures performed in the setting of nondisseminated cancer, but only 0.6% [36/6344] of disseminated cancer cases. The next most frequent procedures in nondisseminated cancer were exploratory laparotomy/laparoscopy (4.4% [139/3172]), cystourethroscopy (4.3% [135/3172]) and hernia repair (4.1% [130/3172]). Among cases with disseminated cancer, the most frequent procedures

TABLE 2 Most frequent surgical procedures for the cancer subgroup stratified by cases with and without disseminated cancer.

Surgical procedure family	Disseminated (*n* = 6344)		Nondisseminated (*n* = 3172)	
	n	%	*n*	%
Colectomy, proctectomy	644	10.2%	649	20.5%
Exploratory laparotomy/laparoscopy, enterolysis, enterotomy, enterectomy	417	6.6%	139	4.4%
Hip/pelvis/proximal femur	397	6.3%	100	3.2%
Cystourethroscopy for tumor	375	5.9%	135	4.3%
Ostomy creation or closure	338	5.3%	104	3.3%
Pneumonectomy	246	3.9%	90	2.8%
Craniectomy for tumor	224	3.5%	15	0.5%
Hernia repair (inguinal, femoral, umbilical, ventral)	210	3.3%	130	4.1%
TURP/laser	185	2.9%	53	1.7%
Hepatectomy	164	2.6%	10	0.3%
Nephrectomy	152	2.4%	22	0.7%
Cervical lymphadenectomy	130	2.0%	69	2.2%
Distal femur/knee	109	1.7%	55	1.7%
Mediastinoscopy	98	1.5%	22	0.7%
Cholecystectomy	95	1.5%	54	1.7%
Pulmonary decortication or pleurodesis	91	1.4%	15	0.5%
Laminectomy for tumor	80	1.3%	9	0.3%
Laryngectomy	71	1.1%	24	0.8%
Pericardiotomy	51	0.8%	11	0.3%
Amputation above knee	49	0.8%	14	0.4%
Gastrojejunostomy	42	0.7%	7	0.2%
Cystectomy	37	0.6%	60	1.9%
Esophagectomy	36	0.6%	291	9.2%

Note: Shaded proportions represent the top five most frequent procedures in each stratum. CPT Family members: Colectomy, proctectomy—44140, 44141, 44143–44147, 44150, 44151, 44155–44158, 44160, 44204–44208, 44210–44212, 45110–45114, 45119–45121, 45123, 45126, 45395, 45397; Exploratory laparotomy/laparoscopy, enterolysis, enterotomy, enterectomy—44005, 44020, 44021, 44025, 44050, 44120, 44125, 44130, 44180, 44202, 44602–44605, 44615, 49000, 49002, 49320, 49321; Hip/pelvis/proximal femur—27059, 27075, 27076, 27078, 27122, 27125, 27130, 27132, 27134, 27138, 27187, 27228, 27235, 27236, 27244, 27245, 27248, 27269, 27280, 27295, 27299; Cystourethroscopy for tumor—52214, 52224, 52234, 52235, 52240; Ostomy creation or closure—44187, 44188, 44227, 44300, 44310, 44312, 44314, 44320, 44322, 44340, 44345, 44346, 44620, 44625, 44626; Pneumonectomy—32440, 32445, 32480, 32482, 32484, 32486, 32488, 32503–32505, 32663, 32665–32667, 32669, 32670; Craniectomy for tumor—61500, 61510, 61512, 61514, 61516, 61518–61521, 61526; Hernia repair (inguinal, femoral, umbilical, ventral)—49505, 49507, 49520, 49521, 49525, 49550, 49553, 49560, 49561, 49565, 49570, 49585, 49587, 49650–49654, 49656, 49657; TURP/laser—52601, 52630, 52640, 52647, 52648; Hepatectomy—47120, 47122, 47125, 47130; Nephrectomy—50220, 50225, 50230, 50234, 50236, 50240, 50543, 50545, 50546, 50548; Cervical lymphadenectomy—38720, 38724; Distal femur/knee—27301, 27303, 27310, 27327–27329, 27334, 27355, 27360, 27364, 27365, 27372, 27446, 27447, 27450, 27454, 27486–27488, 27495, 27506, 27507, 27511, 27513, 27514; Mediastinoscopy—39400; Cholecystectomy—47562–47564, 47600, 47605, 47610, 47612; Pulmonary decortication or pleurodesis—32220, 32225, 32310, 32320, 32650–32652; Laminectomy for tumor—63266, 63267, 63271, 63275–63278, 63280–63282, 63285, 63286; Laryngectomy—31300, 31320, 31360, 31365, 31367, 31368, 31382, 31390, 31395; Pericardiotomy—32659, 32661, 33015, 33025; Amputation above knee—27590, 27592, 27594, 27596, 27598; Gastrojejunostomy—43820, 43825, 43860; Cystectomy—51550, 51555, 51565, 51575, 51585, 51590, 51595, 51596; Esophagectomy—43100, 43101, 43107, 43108, 43112, 43116–43118, 43121–43124.

Abbreviations: *n*, number; % column proportion of cohort.

after colectomy were exploratory laparotomy/laparoscopy (6.6% [417/6344]), surgical repair of hip, pelvis, or proximal femur (6.3% [397/6344]), cystourethroscopy (5.9% [375/6344]) and ostomy closure or creation (5.3% [338/6344]). colectomy/proctectomy.

3.3 | Frailty

For the overall cohort, 10.9% [52 465/480 731] were classified as frail using the complete RAI (Table 3). However, after omitting all

TABLE 3 Frailty status of the entire cohort (n = 480 731) and the cancer subgroup (n = 9516).

	Overall cohort				Cancer subgroup			
	Frail		RAI score		Frail		RAI score	
RAI variant	*n*	%	Mean	SD	*n*	%	Mean	SD
RAI	52 465	10.9%	35.8	5.7	9512	99.9%	39.7	6.1
RAI (without cancer)[a]	46 536	9.7%	36.0	5.4	3583	37.7%	36.2	6.4
RAI (radiotherapy)[b]	47 243	9.8%	35.2	5.4	4288	45.1%	37.9	6.0
RAI (chemotherapy)[c]	47 400	9.9%	35.2	5.4	4445	46.7%	38.0	6.2
RAI (disseminated cancer)[d]	49 846	10.4%	35.6	5.7	6893	72.4%	39.8	6.5

Note: Frailty defined as RAI ≥ 30. Cancer Subgroup defined by the presence of any one of the three cancer-related variables. RAI variants calculated: [a]without any of the cancer-related variables or with only; [b]radiotherapy; [c]chemotherapy, or; [d]diesseminated cancer.

Abbreviation: RAI, Risk Analysis Index.

TABLE 4 Discrimination and calibration of RAI models when applied to the overall cohort and the cancer subgroup.

	c-statistic (95% CI)	*p* Value[a]	Max R^2 (%)	AIC
Overall cohort (n = 480 731)				
RAI	0.842 (0.839–0.845)	REF	25.5	114 881.8
RAI (without cancer)	0.820 (0.817–0.824)	<0.0001	21.8	119 913.9
RAI (radiotherapy)	0.824 (0.821–0.828)	<0.0001	22.4	119 129.0
RAI (chemotherapy)	0.826 (0.823–0.829)	<0.0001	22.6	118 871.0
RAI (disseminated cancer)	0.840 (0.836–0.843)	<0.0001	25.4	115 083.6
Cancer subgroup (n = 9516)				
RAI	0.704 (0.692–0.716)	REF	15.1	10 142.2
RAI (without cancer)	0.695 (0.682–0.707)	<0.0001	14.1	10 215.2
RAI (radiotherapy)	0.625 (0.612–0.637)	<0.0001	6.0	10 785.6
RAI (chemotherapy)	0.632 (0.620–0.645)	<0.0001	6.6	10 748.1
RAI (disseminated cancer)	0.736 (0.725–0.748)	<0.0001	19.3	9828.7

[a]*p* Values compare c-statistics using the methods described by DeLong et al.[16]

cancer-related variables, the RAI (without cancer) score classified 9.7% [46 536/480 731] records as frail, suggesting that most frail cases were frail for reasons other than cancer. Among the cancer subgroup, almost all cases were classified as frail (>99% [9512/9516]) using the complete RAI whereas the RAI (without cancer) classified only 37.7% [3583/9516] as frail, suggesting that among cancer patients, the majority (62.3% [5929/9516]) are classified frail because of the cancer-related variables. The proportions of cancer patients classified as frail increased when each of the cancer-related variables were added to the RAI score with disseminated cancer classifying 72.4% [6893/9516] as frail.

3.4 | RAI model discrimination and calibration

Table 4 provides the univariate logistic regression models predicting postoperative mortality of the entire cohort and the cancer subgroup using the five RAI models. For the overall cohort, the complete RAI model showed the best discrimination (c = 0.842) and calibration (Max R^2 = 25.5%). The omission of any cancer-related variables significantly diminished model discrimination and calibration (all p < 0.0001). The worst calibration was observed in the RAI variant omitting all cancer-related variables (c = 0.820, Max R^2 = 21.8). However, model performance of the RAI variant including only disseminated cancer (e.g., RAI [disseminated cancer]) approached that of the complete RAI model (c = 0.840 vs. c = 0.842 and Max R^2 = 25.5% vs. 25.4%., respectively) Although statistically different due to large sample size, the differences between the four RAI variants and the complete RAI do not likely represent clinically meaningful differences.

In contrast with the overall cohort, the best performing variant in the cancer subgroup was RAI (disseminated cancer), outperforming the complete RAI in terms of discrimination (c = 0.736 vs. 0.704, respectively, p < 0.0001) and calibration (Max R^2 = 19.3% vs. 15.1%, respectively). However, like the overall cohort, the statistical differences between the four RAI variants and the complete RAI

may simply reflect large sample size, warranting caution in interpreting the clinical relevance.

3.5 | Age and frailty in the cancer subgroup

To quantify the impact of the cancer variables on frailty classification across age groups, we stratified the cancer subgroup by age at surgery and calculated their RAI and RAI (without cancer). This comparison distinguishes cases classified as frail *because of the cancer-related variables* (i.e., RAI ≥ 30, but RAI (without cancer) < 30) from those classified as frail *regardless of the cancer-related variables* (i.e., RAI and RAI (without cancer) are both ≥ 30). In the cancer subgroup, 100% [911/911] of patients who were 80+ years old at the time of surgery classified as frail regardless of cancer-related variables, whereas only 4.9% [53/1084] of patients under the age of 55 were classified frail regardless of cancer-related variables (Table 5). Within cancer patients who were 55 through 79 years old at the time of surgery, 34.8% [2619/7512] were classified as frail regardless of cancer-related variables.

To further understand the age-specific performance of the RAI in the cancer subgroup, Table 6 provides the discrimination and

TABLE 6 Discrimination and calibration of RAI models when applied to the cancer subgroup ($n = 9516$) stratified by age.

Model[a]	c-statistic (95% CI)	Max R^2 (%)	AIC
RAI			
<55	0.715 (0.677–0.754)	14.4	969.7
55–79	0.692 (0.679–0.707)	14.3	8041.2
80+	0.682 (0.647–0.717)	12.8	1128.2
RAI (disseminated cancer)			
<55	0.750[b] (0.715–0.786)	18.8	936.5
55–79	0.730[b] (0.717–0.743)	18.6	7787.7
80+	0.700[b] (0.666–0.735)	15.1	1111.5

Abbreviations: AIC, Aikake Information Criterion; Max R2, Maximum rescaled r-squared statistic; RAI, Risk Analysis, Index.

[a]Separate models fit for each age strata where age <55 $N = 1084$, age 55–79 $N = 7251$, and age ≥80 $N = 911$.

[b]Comparison of discrimination of the complete RAI versus the RAI (disseminated cancer) were significant a $p = 0.0349$ for age < 55, $p < 0.0001$ for age 55–79 and $p = 0.0472$ for age ≥ 80.

TABLE 5 Frailty among the cancer subgroup stratified by age at surgery ($n = 9516$).

Age years	Cohort size *n*	RAI Mean (SD)	Frail RAI ≥ 30 (*n*)	Frail regardless of cancer RAI (without cancer) ≥ 30 (*n*)	%
18–24	4	31.5 (0.6)	4	0	0.0%
25–29	20	34.7 (6.4)	16	1	6.3%
30–34	35	32.6 (3.3)	35	0	0.0%
35–39	46	34.2 (4.3)	46	0	0.0%
40–44	118	36.0 (5.3)	118	4	3.4%
45–49	226	36.4 (5.3)	226	13	5.8%
50–54	635	36.9 (4.5)	635	35	5.5%
55–59	1140	38.5 (5.7)	1140	145	13%
60–64	2488	39.1 (5.7)	2488	834	33.5%
65–69	2090	39.7 (5.6)	2090	741	35.5%
70–74	1010	40.9 (5.8)	1010	404	40.0%
75–79	793	41.5 (6.4)	793	495	62.4%
80–84	536	42.9 (6.9)	536	536	100.0%
85–89	312	44.0 (6.7)	312	312	100.0%
90+	63	46.9 (9.2)	63	63	100.0%
Total	**9516**		**9512**	**3583**	

Note: The value of the complete RAI always exceeds the value of the RAI (without cancer), and therefore cases where RAI (without cacner) ≥ 30 can be considered frail "regardless" of the cancer-related variiabes. By contrast those with RAI ≥ 30 but RAI (without cancer) < 30 can be consdiered frail "because" of the cancer-related variables. The number of patients classified as frail "because" of cancer is the difference between the number frail and the number fraiil regardless of cancer.

Abbreviations: *n*, number; RAI, Risk Analysis Index; SD, standard deviation; %, row proportion.

calibration of univariate logistic regression models predicting postoperative mortality of the cancer subgroup, stratified by age, and focusing on the comparison between the RAI and the RAI (disseminated cancer) models. The RAI (disseminated cancer) model showed better discrimination and calibration than the complete RAI model for all three age groups but decreased with increasing age. The best discrimination and calibration were observed with the RAI (disseminated cancer) for cases under 55 years old ($c = 0.750$; Max $R^2 = 18.8\%$).

4 | DISCUSSION

The goal of this retrospective cohort study of VASQIP data was to assess the RAI's power to accurately identify frailty and predict postoperative mortality in cancer patients. We found that, in the overall cohort, most cases (98% [471 215/480,731]) did not represent a cancer diagnosis as defined by the cancer-related variables available in VASQIP. It is likely that patients with one or more of these variables represent only a subset of the entire population of surgical patients with a cancer diagnosis, but VASQIP does not afford a reliable way to estimate this larger sample. Defining cancer status as the presence of any of the three VASQIP variables indicating preoperative malignancy (i.e., disseminated cancer, preoperative chemotherapy, and/or preoperative radiotherapy) is highly specific, but not particularly sensitive, and likely represents more advanced and aggressive tumors. In the overall cohort, RAI discrimination and calibration was strong even when all the cancer-related variables were omitted ($c = 0.820$). We also found that the incremental improvement in model performance associated with cancer-related variables was attributable primarily to the presence or absence of disseminated cancer, and that the discrimination of the model including only this variable [RAI (disseminated)] approached that of the complete RAI model ($c = 0.840$ vs. 0.842). The discrimination of all five RAI variants degraded modestly when the sample was restricted to cancer patients, and in this subgroup, the RAI (disseminated) variant had better discrimination than the complete RAI ($c = 0.736$ vs. 0.704). Among cancer patients, all RAI variants performed best among younger patients, perhaps because all patients ≥ 80 years were classified as frail *regardless* of their cancer diagnosis, whereas 95% (1027/1080) of patients < 55 were frail *because* of their cancer diagnosis. When screening for frailty in cancer populations, the history of cancer (especially disseminated cancer) adds meaningful power to RAI calculations. Within our cancer subgroup, almost all (>99% [9512/9516]) were classified as frail when applying the complete RAI. However, 38% [3,583/9,516] of these were frail regardless of cancer and 67% [6344/9516] had a disseminated cancer, suggesting the possibility of over-classification of cancer patients as frail in only 23% [2228/9516] of cases.

Although it is expected that many patients with neoadjuvant chemo/radiotherapy eventually proceed to the operating room, the benefit of operating on patients with disseminated cancer is less obvious. Although they represent only 1.3% [6344/480 731] of the procedures recorded in this VASQIP sample, there were 6344 cases of surgery in the setting of disseminated cancer. Attempts to cure such patients with extensive, highly morbid procedures would be justified only in specific clinical contexts. Our data lack the detail to analyze the operative intent, but the distribution of procedures for these patients as compared to those without disseminated cancer was reassuring that case selection in the setting of disseminated cancer is appropriately palliative. For example, the overwhelming majority of esophagectomies were performed in the setting of nondisseminated cancer, suggesting appropriate operative planning. Colectomies remained frequent in the setting of disseminated cancer, but this is plausible given the benefits of liver metastectomy at the time of primary resection. In addition, the relatively increased prevalence of ostomy creation, enterolysis and hip fracture repair are all consistent with the symptomatic, palliative management of disseminated disease.

These findings have several implications for direct patient care in surgical oncology settings. First, RAI-derived estimates of frailty in patients with cancer are most reliable in those whose cancer is disseminated because this clinical parameter was used to calibrate the scoring system, consequently providing the best discrimination ($c = 0.736$). Second, for cancer patients ≥ 80 years old, the complete RAI reliably classifies frailty, regardless of cancer diagnosis, and such patients should likely be considered frail independent of tumor type or stage. Third, in younger patients < 55 years old, the cancer diagnosis determines the frailty classification in nearly all cases, and in this context, the frailty classification is most reliable when the patient's cancer is disseminated ($c = 0.750$). Fourth, for patients 55–80 years old, 65.1% [4893/7512] of patients classified as frail are so classified because of the cancer-related variables, and clinical judgment is required to assess whether the cancer diagnosis is determinative of frailty. Finally, for elective surgical indications unrelated to cancer treatment like cholecystectomy or knee arthroplasty, the RAI's sensitivity to potentially disseminated disease may occasion appropriate reconsideration regarding procedures that will not extend survival, and after which patients may succumb to malignancy before accruing the hoped-for benefit of surgery.

These findings also inform the use and interpretation of the prospective RAI survey, which defines cancer status as any cancer diagnosed or treated in the past 5 years. The RAI survey is likely to be more sensitive and less specific, raising the questions about how to interpret the risk/points attributable to the presence of cancer. When the RAI survey is used to screen for frailty at the point of care, we recommend that clinicians calculate both the complete RAI and the RAI (without cancer) for every patient answering the cancer question in the affirmative. This question is broadly worded to maximize the RAI's sensitivity to capturing patients with any cancer diagnosis by asking, "In the past 5 years, have you been diagnosed with or treated for cancer?" If the patient has disseminated cancer, the complete RAI score is most accurate and reliably predicts outcomes. If the tumor type or stage indicates a prognosis in years rather than months (e.g., basal cell carcinoma or early colon cancer), the RAI (without cancer) is probably a more accurate estimate of frailty. For cancer patients

whose tumor type and stage are of intermediate significance, the choice of most appropriate RAI score requires honest introspection on the part of the surgeon regarding the most likely outcome of surgical treatment. For cancer patients whose tumor type and stage suggest a surgical cure is possible, but unlikely (e.g., pancreas adenocarcinoma), the complete RAI is probably the more accurate estimate of frailty. Regardless, computing and considering both the complete RAI and RAI (without cancer) exposes to the clinician the impact of the cancer diagnosis on frailty, informing clinical judgment. If both scores exceed the frailty threshold, the question is moot and the patient should be considered frail. Discrepancy between the scores indicates the need for careful clinical judgment.

Finally, these findings inform the application of the RAI to the ACS NSQIP. Although prior work validated the RAI in a large sample of 1.4 million patients recorded in ACS NSQIP from 2005 to 2014, variables for preoperative chemotherapy and radiation treatment were phased out after 2014, making it impossible to calculate the complete RAI as originally described.[7,8] However, the ACS NSQIP retains the variable for disseminated cancer, and since the RAI (disseminated cancer) variant has almost identical discrimination and calibration compared to the complete RAI, we recommend that investigators interested in using the RAI in ACS NSQIP use all cancer-related variables when available, but exclude only those cases that are missing all three variables. This approach has been previously validated for RAI computation of cognitive status that relies, in part, on variables phased out of NSQIP in 2012.[17]

Frailty is a unique geriatric concept that quantifies overarching physiologic reserve and is strongly associated with adverse health outcomes in adults having elective cancer surgery.[18] Frailty assessment has been demonstrated to add value beyond other standard measures of preoperative risk with frailty found to be associated with worse postoperative complications, higher rates of discharge to rehabilitation, and higher rates of postoperative hospitalization > 30 days in older patients undergoing colorectal cancer resection independent of their American Society of Anesthesiologist Physical Status Classification System (ASA grade) status.[19] Further, the addition of objective biomarkers like albumin, hematocrit, or serum creatinine does not yield clinically meaningful improvements in predictive power over and above what is rendered by the RAI survey.[20] The RAI survey has been shown feasible for screening large, ambulatory populations in a median 30 s to provide an initial estimate of physiologic reserve available to clinicians in real time to guide clinical decisions.[8,9]

4.1 | Limitations

This study has several limitations that should temper its interpretation. First, some clinicians may find it cumbersome to interpret the scores simultaneously (e.g., the RAI with and without cancer variables). However, the intended purpose of the RAI is to enhance rather than replace clinical judgment, and rather than foreclosing the interpretation of the cancer-related variables, we have presented cancer-specific details so that clinicians can interpret for themselves the significance of cancer status. Second, each record within VASQIP represents a unique case not a unique patient, so patients who underwent more than one noncardiac surgery during the study period would appear more than once in our data set. Second, patients in VASQIP do not reflect the make-up of the civilian surgical population (especially in the distribution of sex), so results from this data set may not generalize outside the Veteran population. Third, the large sample size provided enormous statistical power to detect differences in c-statistics that may not be clinically meaningful, and thus caution is warranted when interpreting the differences in discrimination observed across the RAI variants. Fourth, VASQIP does not include important details regarding cancer type and stage that have significant effects on treatment options and overall prognosis. Finally, like many large registry databases, VASQIP limits the ability to determine indications for specific procedures with confidence; thus, it is unclear which patients with cancer received cancer-directed operations. A future study using more detailed information to determine oncologic indications for surgery, surgical type, cancer type and stage would be more helpful in studying the relationship between malignancy and RAI score in postoperative outcomes; our group is working to carry out such a study. Despite these limitations, this study provides valuable insight into the interpretation and application of the RAI in cancer patients.

5 | CONCLUSION

The complete RAI is robust for screening frailty in heterogenous populations where cancer status adds to its predictive power. Among cancer patients, the complete RAI demonstrates somewhat less discrimination, but remains a strong predictor of postoperative mortality, especially in the setting of disseminated cancer. However, in cases where surgical intent is curative, clinical judgment is required to apply either the complete RAI or the variant RAI (without cancer).

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DATA AVAILABILITY STATEMENT

The data for this study are not publicly available due to the terms of the VASQIP data use agreement.

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