2020 CAS Annual Meeting

Residents' Oral Competition
(abstracts)

Contents

BNP as a Screening Tool for Myocardial Infarction and Myocardial Injury after Noncardiac Surgery

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Background: Major cardiac complications are responsible for at least a third of perioperative deaths and are associated with significant morbidity (1-3). Canadian Cardiovascular Society (CCS) Guidelines on Perioperative Cardiac Risk Assessment identify B-type natriuretic peptide (BNP) ≥ 92 ng/L as an independent predictor of myocardial infarction (MI) up to 30 days after surgery (4). CCS guidelines recommend screening with preoperative BNP and measuring daily high-sensitivity troponin up to 72 hours after surgery when BNP ≥ 92 ng/L. Without cardiac biomarker screening, more than half of all perioperative myocardial infarctions go undetected (4) (5). This silent ischemia is termed myocardial injury after non-cardiac surgery (MINS) (5). It is defined as troponin T ≥ 0.03 ng/ml (4). MINS has been associated with significantly increased 30-day mortality (6).

Objectives:

1. Compare the rates of myocardial infarction in the first 30 days after surgery in BNP positive and negative patients
2. Determine the incidence of MINS in the first 72 hours after surgery in BNP positive patients
3. Explore the current management strategy of MINS

Methods: Ethics approval was obtained from the local REB and the study was registered at clinicaltrials.gov (NCT04077294). Patients undergoing elective, noncardiac surgery with an overnight stay were assessed at the Preadmission Clinic. BNP screening was performed in patients who qualified according to CCS guidelines (4). Patients with positive BNP underwent postoperative cardiac monitoring with daily high-sensitivity troponin I (hsTnI). All patients were contacted by telephone at 30 days after surgery to determine incidence of myocardial infarction. Medical records were reviewed if patients had an MI or MINS. Fischer's exact test was used to compare the postoperative incidence of MI between BNP positive and negative patients.

Results: 1348 elective surgical patients were screened in the preadmission clinic between May 21st and September 12th, 2019. 287 patients (21.3%) qualified for BNP measurement. 70/287 (24.3%) patients had positive BNP. The incidence of MI within 30 days for BNP positive patients was 2.2% (1/70) and in BNP negative patients was 0.5% (1/217). This was not statistically significant ($p=0.429$). 25 patients were excluded because low sensitivity troponin was measured postoperatively leaving 262 patients for analysis. 13.3% (6/45) of BNP positive patients had MINS within 72 hours of surgery. None of the MINS patients had an MI or died within 30 days of surgery.

Conclusion: Preoperative BNP screening of at-risk patients undergoing noncardiac surgery was not found to be a valuable tool for predicting patients at risk of postoperative MI. Even though preoperative BNP screening was useful for detecting patients at risk of MINS, we found no evidence of increased cardiac morbidity or mortality in this population.

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Derivation and External Validation of A 30-Day Mortality Risk Prediction Model for Older Patients Having Emergency General Surgery

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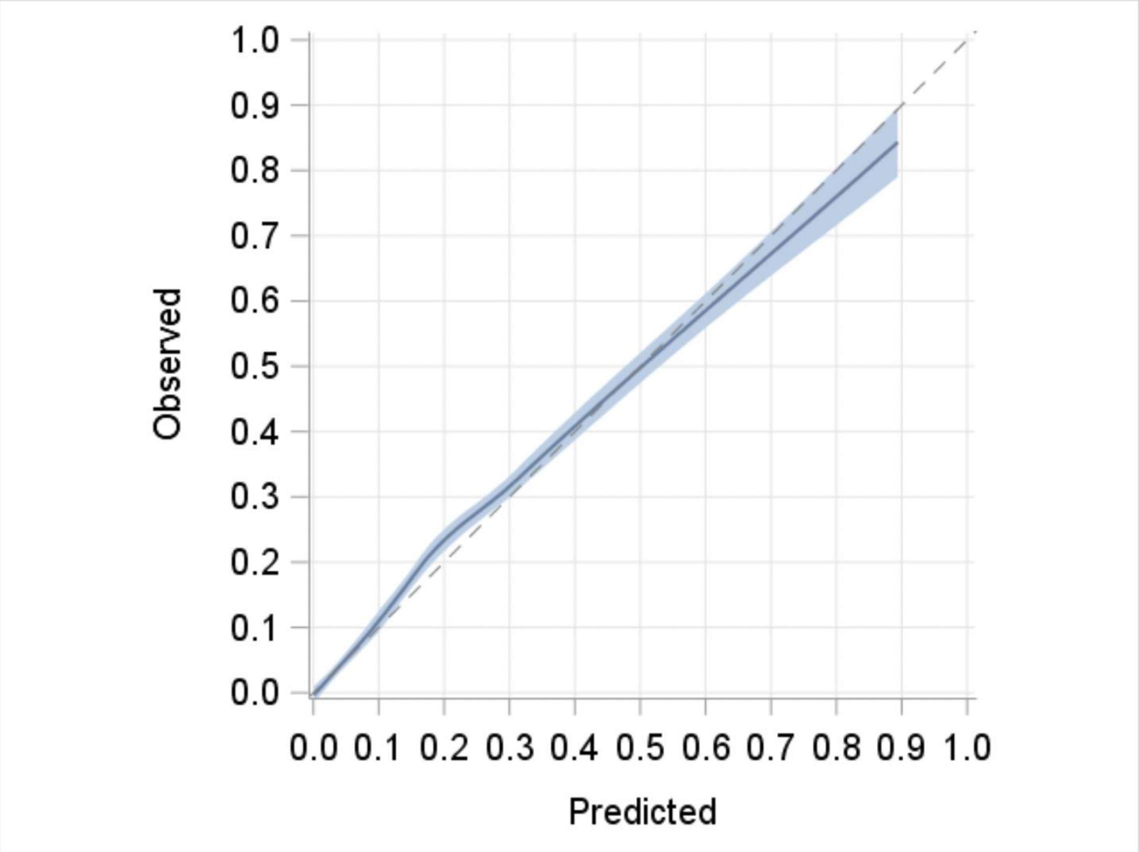
Introduction: People ≥65 years old are over-represented among patients who require emergency general surgery (EGS)[1,2]. These high-risk patients are often medically complex and near the end of life,[2] creating prognostic and decisional uncertainty. Accurate risk prediction models can support informed consent and ensure clinical decisions align with goals of care. However, current preoperative risk prediction models for older EGS patients have major limitations, and do not address the specific risk profile of older patients[3–6]. Accurate and externally validated models specific to older patients are needed to inform care and decision making. The objective of this study is to derive, internally and externally validate a multivariable model to predict 30-day mortality in EGS patients ≥65 years old.

Methods: Ethics approval to use National Surgical Quality Improvement Program (NSQIP) data was obtained from the local REB. External validation will use routinely collected anonymized data that are legally exempt from research ethics review. This retrospective cohort study included 50,221 patients from the NSQIP database having 1 of 7 core EGS procedures (appendectomy, cholecystectomy, laparotomy, lysis of adhesions, large and small bowel resection, and peptic ulcer repairs). Predictor variables were pre-specified based on clinical and epidemiological knowledge. Outcome was 30-day all-cause mortality from the index surgical procedure. The model was derived using logistic regression penalized with elastic net regularization, as well as a machine learning technique called ensemble modelling to aggregate results across 5000 bootstrap samples and reduce overfitting. The model was internally validated with k-fold validation (k=10) and bootstrap internal validation. Secondary analysis was done including pre-specified lab variables with complete case elastic net regularization analysis. Multiple imputation analysis was done for missing variables. External validation is being conducted using a provincial health database.

Results: Of the 50,221 patients ≥65 years old having EGS procedure between 2012-2016, 6,218 (12.4%) died. Factors associated with mortality include older age, frailty and related characteristics, higher risk surgery, and comorbidities. After tuning of our elastic net logistic regression model, we achieved strong discrimination (area under the curve [AUC] 0.871) and calibration (agreement between observed and predicted risks across the spectrum using Loess-smoothed calibration plots, **Figure 1**). Internal validation achieved a range of AUC consistent with derivation (K-fold AUC 0.850-0.885, Bootstrap AUC 0.870) with similar Loess-smoothed calibration plots. Addition of lab-based predictors (AUC 0.871) did not improve model discrimination or calibration.

Conclusion: Derivation and internal validation of a multivariable mortality risk prediction model specific to older people having EGS demonstrated strong discrimination and calibration. A planned external validation is currently underway. Following external validation, clinical testing will be required to evaluate whether this model can support improved decision making for high risk older patients having emergency general surgery.

Figure 1 – Loess smoothed calibration plot of observed vs. expected risk of 30-day mortality



The Loess smoothed calibration plot for the logistic regression model with elastic net regularization shows strong calibration across the entire spectrum of observed versus predicted risk of 30-day mortality.

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Dose-Dependent Effects of Protamine on Coagulation and Platelet Function in The Context of In Vitro Heparin Reversal

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Introduction: Protamine is the agent of choice for reversal of unfractionated heparin (UFH) in the context of cardiopulmonary bypass (CPB). The current practice consensus of protamine-to-heparin-dosing-ratio (P:H) for adequate reversal is 1:1 [1]. Increasingly, studies highlight the paradoxical bleeding risk from excess protamine, favouring a lower P:H [2]. At concentrations suitable for CPB, UFH (4 international units (IU)/mL) is known to inhibit coagulation and thrombin generation [3]. Contrarily, protamine's anti-platelet and anti-coagulation effects have not been fully characterized at clinically relevant concentrations.
We evaluated the *in-vitro* impact of clinically relevant concentrations of protamine with 4 IU/mL UFH in whole blood (P:H = 0.5:1; 1:1 and 1.5:1) on platelet function, intrinsic pathway coagulation, and thrombin generation.

Methods: Ethics approval was obtained from the local REB. Protamine (0, 20 ug/ml, 40 ug/ml, 60 ug/ml) and UFH (0, 4 IU/mL) in P:H of 0:1; 0.5:1; 1:1;1.5:1 and 1.5:0 were added to venous blood collected from consented healthy volunteers (n = 10). Post-incubation (5 minutes, at room temperature) samples were assayed for global measures of intrinsic coagulation in clotting times (CTs) with Thromboelastometry (ROTEM-INTEM and HEPTEM), platelet function (Plateletworks) and thrombin generation (Calibrated Automated Thrombography, CAT). Paired t-tests were applied to detect statistical significance between variable groups from baseline (no heparin or protamine).

Results: Higher P:H of 1:1 and 1.5:1 showed significant prolongation of CTs compared to baseline CTs (250 secs ± 19 and 275 ± 49 vs 189 ± 20; p= 0.016 and 0.0001 respectively), while P:H of 0.5:1 showed no significant change in CTs. Heparin neutralisation using P:H of 1:1 and 1.5:1 significantly impaired recovery of thrombin generation to baseline, as measured by endogenous thrombin potential (ETP= 1059 nM*min ± 22.3 and 1214 ± 38.1 vs 1406 ± 44.0; p= 0.013 and 0.001) and peak thrombin generation (Peak= 118 nM ± 3.3 and 143 ± 3.8 vs 247 ± 8.1; p= 0.001 and 0.004) when compared with low P:H of 0.5:1. No appreciable platelet dysfunction was detected in all experimental groups after collagen mediated platelet activation using Plateletworks.

Conclusion: Our study shows that *in vitro* doses of protamine considered to be within current standards of care may lead to coagulation impairment. The clinical relevance of these findings needs to be explored.

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Glycemic Control in Diabetic Patients Undergoing Elective Surgery: A Feasibility Study Evaluating Perioperative Subcutaneous Basal Bolus Insulin Therapy

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Introduction: Guidelines recommend blood glucose (BG) values of 5.0 - 10.0 mmol/L for diabetics undergoing non-cardiac surgery without defining an optimal insulin strategy (1). Although variable-rate insulin infusions (VRI) are the perioperative standard, subcutaneous basal-bolus insulin therapy (BBIT) is associated with more cost-effective and efficacious glycemic control in non-ICU patients, and has been recommended for intraoperative use in a recently published review (3, 4). To date, no studies have examined the use of BBIT in the intra-operative and post-anesthetic care setting (PACU).

Objectives: To determine whether BBIT is a feasible alternative to insulin infusions in surgical patients by comparing 1) perioperative BG values and 2) frequency of hyperglycemic (BG >10 mmol/L) and hypoglycemic (BG < 5 mmol/L) events.

Methods: Ethics approval was obtained from the local REB for this non-randomized, prospective study (Pro 00077714). Patients who met eligibility criteria (insulin-dependent diabetes (Type 1 and 2), elective surgery < 4 hours duration and Hgb A1C < 10% within 90 days before surgery) were consented, and patients with significant hepatic disease, renal failure with GFR < 30, expected large fluid shifts during surgery, or post-operative ICU admission were excluded. Staged recruitment for the BBIT group was followed by that of the VRI group over 8 months. BBIT participants reduced their last dose of basal insulin before surgery and received rapid-acting subcutaneous insulin intra-operatively according to a previously published regimen (4). Capillary BG was measured pre-operatively and every 1-2 hours until discharge from the PACU per protocol. VRI participants received our institution's standard intravenous insulin protocol and monitoring. A two-sample t-test and Fisher exact test were used to analyze the collected data.

Results: Twenty BBIT and 21 VRI patients were recruited. Two outliers with significant hyperglycemia (one in each group) were excluded from further analysis. Pre-operative, intra-operative and PACU mean BG (mmol/L +/- 95% CI) in the BBIT group were 8.3 +/- 1.07 (SD 2.38), 7.6 +/-1.17 (SD 2.60), and 7.9 +/-1.04 (SD 2.12), respectively. Analogous BG values in the VRI group were 8.4 +/- 1.28 (SD 2.91), 8.3 +/- 1.89 (SD 3.62), and 9.4 +/- 1.35 (SD 3.09). Two-sample t-testing found no difference in mean BG between the BBIT and VRI groups pre-operatively (p=0.954), intra-operatively (p=0.507), and post-operatively (p 0.102). Similarly, a Fisher exact test showed no difference in the number of patients in either group with hyperglycemia or hypoglycemia pre-operatively (p=0.237), intra-operatively (p=0.173), or post-operatively (p=0.195). However, a trend was observed toward lower mean BG with less variation in the BBIT group (Figure 1).

Conclusion: No difference was found between BBIT and insulin infusion groups for the primary and secondary outcomes of BG values and frequency of hyper- or hypoglycemic events. However, trends toward lower glucose values in the BBIT group should be explored in a future study.

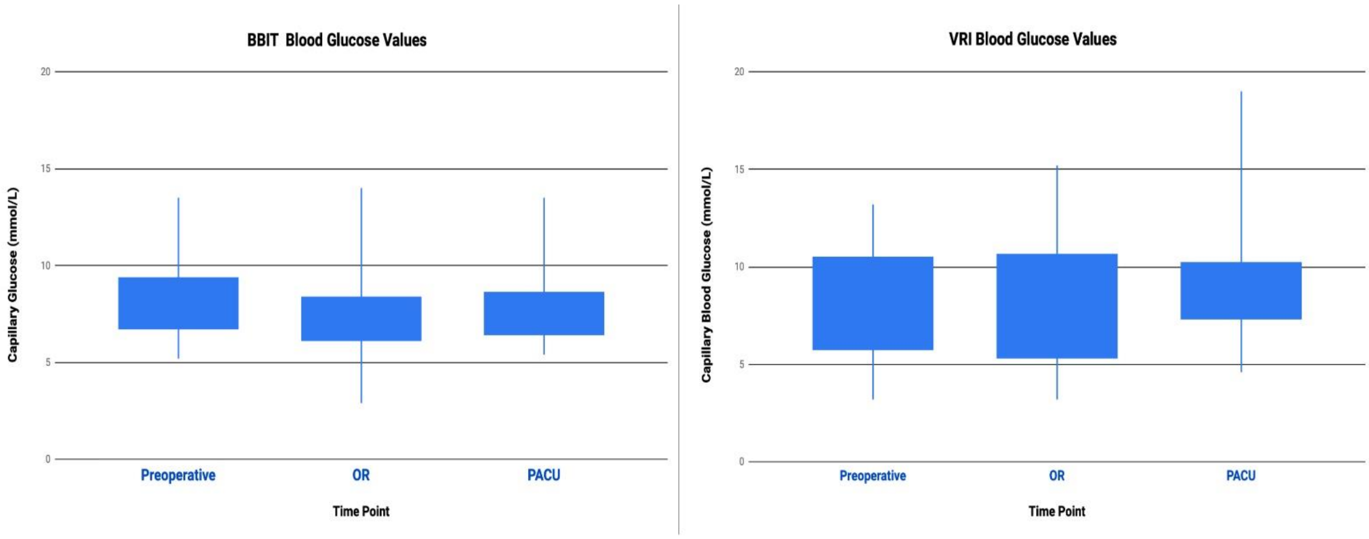

Figure 1. Box-plot comparing blood glucose values in the pre-operative, intra-operative (OR) and post-anesthetic care unit (PACU) period for BBIT (left) and VRI (right) groups. Lower and upper box boundaries represent the 25th and 75th percentiles, respectively, and lower and upper error lines represent the maximum and minimum glucose values.

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Low-Dose Ketamine as an Adjunct to Electroconvulsive Therapy Does Not Improve Psychiatric Outcomes: A Randomized Controlled Trial

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Introduction: Electroconvulsive therapy (ECT) is a well-established therapy for Major Depressive Disorder (MDD). Literature suggests that ketamine at low doses may be an alternative therapy for treatment-resistant MDD1. We hypothesized that the addition of low-dose ketamine to anesthesia for ECT would improve depression scores in patients diagnosed with MDD.

Methods: Ethics approval was obtained from the local REB. Patient consent was acquired and off-label use of ketamine was approved by Health Canada for this randomized, double-blinded, placebo-controlled study. Primary outcome was the number of treatments required to achieve a 50% reduction in the Montgomery-Asberg Depression Rating Scale (MADRS). Secondary outcomes included the number of treatments required to achieve a 25% reduction in MADRS, and differences in Clinical Global Impression Scale for Severity (CGI-S), mean arterial pressure (MAP), heart rate (HR), and seizure duration. Sample size calculation revealed 14 patients per group was required with 80% power and alpha = 0.05. The ketamine dose was increased to 0.5 mg/kg IV (from 0.2 mg/kg) based on the results of a pre-planned interim analysis after the first 14 recruits. Patients received the study drug prior to propofol induction for each ECT treatment, up to a maximum of 12 treatments.

Results: A total of 45 patients completed the study. There was no difference in the number of ECT treatments required for a 50% reduction of MADRS between ketamine (n=16) and placebo (n=15) (8.25 ± 2.72 vs. 7.73 ± 2.89; p=0.56). There was no difference in the number of ECT treatments required for a 25% reduction of MADRS (4.25 ± 1.52 vs. 5.47 ± 2.94; p=0.34); CGI-S (3.75 ± 2.99 vs. 4.73 ± 2.29; p=0.26); seizure duration (35.74 ± 11.82 vs. 35.09 ± 6.97 sec; p=0.85); and peak MAP or peak HR (% above baseline) (125.5 ± 10.2 vs. 122.7 vs. 9.7; p=0.44, and 115.9 ± 14.6 vs. 111.8 ± 13.7; p=0.42, respectively). There was a trend towards decreased propofol dose required in the experimental group (1.13 ± 0.31 vs. 1.36 ± 0.39 mg/kg; p=0.08). No adverse events were reported.

Discussion: Our results suggest the adjunctive use of ketamine does not improve psychiatric outcomes following ECT. Similar hemodynamic profiles and absence of adverse events suggest that low-dose ketamine may be safely used in this setting; however, even in the presence of potentially reduced propofol dosing in the treatment group, there was no increase in seizure duration. Therefore, indications for use of ketamine in ECT should be limited to those that are patient-specific and not for the goal of therapeutic benefit. While ketamine in isolation may be a useful therapy for MDD, the possibility of a therapeutic “ceiling effect” with ECT may explain why the addition of ketamine did not improve therapeutic outcomes in our study.

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The Accuracy and Feasibility of Clinically Applied Frailty Instruments Before Surgery: A Systematic Review and Meta-Analysis

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Introduction: A barrier to routine preoperative frailty assessment is the large number of frailty instruments described. Previous systematic reviews estimate the association of frailty with outcomes, but none has evaluated outcomes at the individual instrument level or specific to clinical assessment of frailty, which must combine accuracy with feasibility to support clinical practice. Lack of clear data on which instrument to use is a recognized barrier to uptake of international guideline-recommended preoperative frailty assessment for all older patients. Therefore, our objective was to systematically review prospective preoperative clinical frailty assessment to determine the instrument-level feasibility and association with high priority outcomes.

Methods: Ethics approval was not applicable because the study did not involve human or animal research. We conducted a pre-registered systematic review (CRD42019107551) of studies prospectively applying a frailty instrument in a clinical setting prior to surgery. Medline, EMBASE, CINAHL and Cochrane databases were searched using a peer-reviewed strategy. All stages of the review were completed in duplicate. The primary outcome was mortality, secondary outcomes included complications, discharge disposition, delirium, length of stay and functional recovery. Effect estimates were pooled using random-effects models. Risk of bias was assessed. Feasibility measures were collected and qualitatively synthesized using directed content analysis.

Results: Seventy studies were included; 45 contributed to meta-analyses. Frailty was defined using 35 different instruments; five instruments had data from at least 3 studies, allowing meta-analysis. The Fried Phenotype was most often studied. Most strongly associated with: mortality and non-favourable discharge was the Clinical Frailty Scale (OR 4.89, 95%CI 1.83-13.05 and OR 6.31, 95%CI 4.00-9.94, respectively); complications the Edmonton Frail Scale (OR 2.93, 95%CI 1.52-5.65); and delirium the Frailty Phenotype (OR 3.79, 95%CI 1.75-8.22). Thirty-two studies reported aspects of feasibility, and the Clinical Frailty Scale, Edmonton Frail Scale, Frailty Index, and Frailty Phenotype had the most data. The Clinical Frailty Scale had the highest reported measures of feasibility, specifically reported to be fast and easy to use with minimal logistical or environmental barriers. All available data positively supported the Clinical Frailty Scale, the Edmonton Frail Scale and Frailty Index had

predominantly positive ratings, however majority of the data for the Frailty Phenotype did not support feasibility.

Conclusion:

Preoperative frailty assessment is a guideline recommended aspect of optimal preoperative care for older people. When choosing a frailty instrument, clinicians should consider accuracy and feasibility. Based on our review of seventy studies, strong evidence in both domains supports the Clinical Frailty Scale, while the Fried Phenotype may require a trade-off of accuracy with lower feasibility.

See supporting data below.

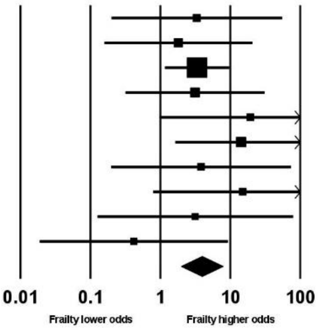
a)

Association of Frailty Phenotype with Mortality

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Ad 2016	3.320	0.202	54.694	0.839	0.401
Huded 2016	1.810	0.160	20.473	0.479	0.632
Kristjansson 2012	3.350	1.170	9.591	2.253	0.024
Lytwyn 2017	3.130	0.320	30.658	0.980	0.327
Revenig 2013	19.340	0.981	381.259	1.947	0.051
Revenig 2015	14.270	1.647	123.612	2.413	0.016
Gleason 2017	3.820	0.199	73.230	0.889	0.374
Pelavski 2017	15.041	0.794	284.957	1.806	0.071
Kapoor 2017	3.160	0.127	78.555	0.702	0.483
Brown 2016	0.417	0.019	9.162	-0.555	0.579
	3.949	1.997	7.808	3.949	0.000

Statistics for each study

Odds ratio and 95% CI



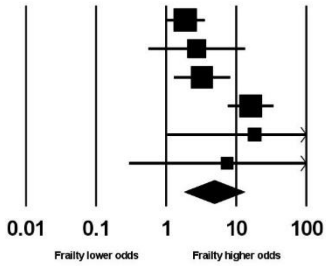
b)

Association of Clinical Frailty Scale with Mortality

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Afilalo 2017	1.870	0.989	3.536	1.926	0.054
Goeteyn 2017	2.730	0.562	13.269	1.245	0.213
Rodrigues 2017	3.246	1.290	8.172	2.500	0.012
Reichart 2018	16.050	7.601	33.893	7.278	0.000
McGuckin 2018	18.351	1.041	323.440	1.988	0.047
Donald 2018	7.442	0.297	186.697	1.221	0.222
	4.889	1.832	13.052	3.168	0.002

Statistics for each study

Odds ratio and 95% CI



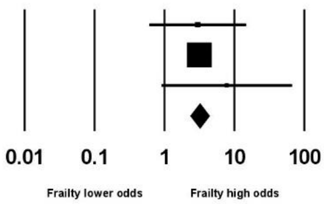
c)

Association of Physical Frailty with Mortality

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Pelavski 2017	2.990	0.610	14.663	1.350	0.177
Afilalo 2016	3.160	2.308	4.326	7.178	0.000
Afilalo 2010	7.780	0.913	66.267	1.877	0.061
	3.212	2.367	4.357	7.497	0.000

Statistics for each study

Odds ratio and 95% CI



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