Perioperative Impact After Non-cardiac Surgery of Physical Activity on Short- and Long-term Morbidity and Mortality NCT06678360

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Statistical Analysis Plan for PeriopIPA

Hypothesis

This cohort study investigates if higher levels of self-reported physical activity at preoperative assessment is associated to lower risk of complications and lower mortality.

Study population

Patients that are ≥18 years old and have undergone elective non-cardiac surgery at the two study sites, Karolinska University Hospital Solna and Karolinska University Hospital Huddinge. Exclusion criteria are transplant, day surgery, acute surgery, anesthesia monitoring, brachy therapy and gamma knife interventions. In case of multiple surgeries, only the first will be included.

Exposure

The Metabolic Equivalent of Task Score (MET-score), reported in the electronic health record by the attending anesthesiologist based on patient history in conjunction with the preoperative assessment.

Outcome

- Death within 30, 60, 90 and 365 days after index surgery.
- Days at home alive (DAH) within 30, 90 and 365 days after index surgery.

Data management

Raw data will be extracted from electronic health records and will be stored as multiple csv or excel on an encrypted hard drive. This will be stored at a secure location since it contains sensitive information according to department routines. The files will be pseudonymized. Using Rstudio the files containing raw data will be merged to create a dataset containing the exposure, the outcomes and relevant patient characteristics.

Statistical analysis

All available data will be extracted for this study, creating a fixed population size and precluding the need for a power calculation. All variables will be explored using distributions and summary measures to make sure that they are assigned the correct type (numerical, categorical) and are appropriately categorized. All covariates will be summarized using the median and interquartile range for continuous variables and count and percentages for categorical variables in a Table. All analysis will be done using complete case analysis.

The exposure and outcome

The exposure variable, MET-scores will be primarily coded as a categorical variable with the levels 1, 2-3, 4-5, 6-8, ≥9 but also explored as a binary variable with the levels <4 and ≥4 (according to clinical guidelines) . Binary variables will be created that indicate death with the levels yes or no and numerical variables that indicate the number of postoperative days to death. Data regarding admission, start of anesthesia and discharge is specified down to the minute. Due to the high resolution of this data the outcome days at home alive (DAH) 30, 90 and 365 will be calculated to the minute and will be defined as a bounded numerical variable rather than a count variable. DAH will be calculated by subtracting the total amount of time hospitalized from the totality of different time frames after index surgery (30, 90 and 365 days). If death occurs within the prespecified time frames the total number of days between the date of death and the end of the time frame will be treated the same as “hospitalized time”.

Distributions will be explored for the exposure and the outcome variables individually and for them against each other. Kapplan-Meier analysis will be done to describe the survival function up to 30, 60, 90 and 365 days after index surgery, for each level of the MET-score variable. This will be presented as two graphs that extend 30 and 365 days, respectively. A Cox regression model will be used to analyze the unadjusted association between MET-score and 30- and 365-day mortality. A multivariate model will be used to analyze the adjusted association between MET-score and 30- and 365-day mortality. The model will be adjusted for age, American Society of Anesthesiologists (ASA), body mass index (BMI) and Surgical risk (according to European Society of Cardiologists 2022 guidelines for non-cardiac surgery) based on domain knowledge (1). The model assumption of proportional odds will be tested, if violated other modeling approaches will be pursued. Results will be presented as hazard ratios and absolute risk difference at 30 and 365 days in a Table.

The association between MET-score and DAH will be analyzed using a logistic quantile regression model (2). This is because DAH will be treated as a bounded numerical variable. A univariate model will be created to analyze the unadjusted association between MET-score and DAH. To best describe the distribution of the outcome variable models will be created for quantiles 0.1 to 0.9 with 0.1 intervals. The logistic transformation will be reversed for all models and the results will be presented as a graph with quantiles on the x-axis and DAH on the y-axis. The same process will be repeated using multivariate models adjusting for the same covariates as for the survival analysis.

The following sensitivity analyses will be performed to explore the robustness of the results:

- If missing values for any important covariate in the models described above exceed 10 %, and missing is believed to be at random, multiple imputation will be performed. The analysis mentioned above will then be redone using imputed data.
- The survival analysis will be repeated on data stratified by the surgical risk variable (described above) to explore if MET-score impacts mortality differently in different sub-types of elective non-cardiac surgery.
- The association between MET-score and DAH will be studied after excluding patients who died within the prespecified DAH time frames to see how much the results found in the original analysis is impacted by mortality.

The alpha significance level will be set at 0.05. All statistical analysis will be performed using Rstudio.

Reference:

1. Halvorsen S, Mehilli J, Cassese S, Hall TS, Abdelhamid M, Barbato E, et al. 2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery. European heart journal [Internet]. 2022 Oct 14 [cited 2022 Nov 14];43(39). Available from: https://pubmed.ncbi.nlm.nih.gov/36017553/

2. Bottai M, Cai B, McKeown RE. Logistic quantile regression for bounded outcomes. Statistics in Medicine. 2010;29(2):309–17.