WARD - Circadian analysis

Clinicaltrials.gov identifier NCT05347784

Statistical analysis plan

Version 1.1

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Method

Patients

This analysis is a part of the Wireless Assessment of Respiratory and circulatory Distress (WARD) project.

The study is a nested case-control study, using patient vital sign data from 3 previous observational cohort studies of postoperative patients.

Clinicaltrials.gov identifiers:

- NCT03491137 (n=491)
- NCT04473001 (n=70)
- NCT04628858 (n=40)

All patients in the studies above have had the following vital signs recorded:

- Heart rate (HR)
- Respiration frequency (RF)
- Peripheral arterial oxygen saturation (SpO_2)
- Blood pressure (BP).

All values except BP have been recorded continuously with a 1-minute sampling rate. BP was recorded every 30 minutes during the daytime and every 60 minutes during the night.

Manual intermittent vital sign measurements were collected from electronic health records for study NCT03491137, and National Early Warning Score values will be calculated from these.

Outcomes

The primary outcome defining the case population is patients that have any postoperative serious adverse event (SAE) occurring from the start of vital sign monitoring in the ward, and up to 24 hours after vital sign monitoring. The control population will be the patients that have no recorded postoperative SAE up to 30 days after surgery. For patients with several outcomes, only measurements in the 24-hour period

preceding the first SAE were chosen for analysis. We also censored the last hour before an outcome, as this time is expected to represent the delay between clinical suspicion and confirmation by a diagnostic test for the specific SAE. For the population with no 30-day SAE, all recorded 24-hour periods were used to calculate exposure variables.

Outcomes for all studies were assessed using a standardised manual that was constructed before outcome evaluation. The definition of an SAE was taken from good clinical practice guidelines:

> "any untoward medical occurrence that at any dose: – results in death,– is life-threatening,– requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a medically important event or reaction.".

Circadian definitions

Six different 'windows' of circadian rhythm were defined from the literature: night-time nadir, peak-to-trough, morning activation, daytime acrophase, afternoon local minimum, and evening deactivation.

Exposures

The primary exposure is the lowest vital sign values at night-nadir, as these values are thought to represent a period of least physiologic stress, and unbiased from movement, and other voluntary activity. Secondary exposures are the lowest vital sign values at the other circadian windows. We also include manually measured NEWS values in the secondary analyses.

Analyses

We did not perform a power analysis prior to analyses due to the nested case-control design.

To avoid calculating values for circadian windows with only limited data, we introduced a minimum data condition, requiring 66 % of data for a specific window-vital sign combination.

A p-value of <0.01 was considered significant to account for multiple statistical testing.

Primary analysis

The primary analysis is descriptive

Secondary analyses

Secondary analyses were a calculation of risk ratios (RR).

For this, Youden's optimal cut-off values will be calculated for each window-vital sign combination.

Afterwards, values for each patient are split into above or below Youden's optimal cut-off point, and risk ratios will be calculated from this discrimination.

For NEWS measurements, a cut-off was defined as a total NEWS score ≥ 6 or a single-parameter score of 3.

Sensitivity analysis

We will also include calculations of fitted cosine curves to vital values, from which rhythm-adjusted mean value (MESOR) and amplitude can be calculated.