A descriptive study of the relationship between preoperative body temperature and intraoperative core temperature change in adults under general anaesthesia

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Abstract

Background: Despite numerous guidelines on perioperative temperature management, perioperative hypothermia remains common. Prewarming to prevent redistribution hypothermia is supported by evidence, but not widely practiced. We investigate the measurement of preoperative mean body temperature as a potential tool for individualising the practise of prewarming.

Methods: We hypothesised that patients who experience intraoperative hypothermia have a lower preoperative mean body temperature. A longitudinal study was conducted in adult patients presenting for ophthalmological surgery under general anaesthesia, to describe the relationship between the incidence of hypothermia within the first hour of anaesthesia and preoperative mean body temperature.

Results: Sixty-five patients were enrolled. Twelve participants (18%) presented to the operating theatre hypothermic (core temperature <36.0°C). A further twenty-eight (43%) became hypothermic during the procedure. All hypothermia events occurred within sixty minutes after induction of anaesthesia, and half of the events occurred within nineteen minutes. The difference in preoperative mean body temperature between those with- and without intraoperative hypothermia was only -0.2°C (95% CI -0.4, 0.1). This is neither clinically relevant nor statistically noteworthy. In Cox proportional hazards analysis, BMI and ASA status compounded the observed association between preoperative mean body temperature and the incidence of intraoperative hypothermia. A higher BMI and ASA are associated with a lower incidence of hypothermia.

Conclusion: We conclude that intraoperative hypothermia is common and occurs early after induction of anaesthesia. We observed no useful difference in preoperative mean body temperature to help distinguish between patients who become hypothermic and those who do not. Without a useful risk prediction tool, a generic approach to prewarming remains appropriate. Preoperative screening for pre-existing hypothermia should be practiced, even in cases considered as low risk.

Declaration

I, Dr Francois Steyn, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signature: Signed by candidate

Date: 28.06.2021

Word Count declaration

This Dissertation has a word count of 16342. The words in tables, figures and references were not included in the word count.

Format of the Dissertation

As per the UCT Faculty of Health Sciences guidelines, the dissertation is submitted in the 'publication-ready format'. It consists of three independent sections.

Part A includes a brief overview and a focused research protocol.

Part B contains the accepted manuscript as per the format of SAJAA.

Part C includes all the supplementary and supporting documents.

References are provided at the end of each section with a complete bibliography also available in part C.

A detailed content section can be found on pages 4 – 6 and lists of tables and figures follow on page 7.

Should the reader wish to cover the critical content of this research in the most expeditious manner, they are encouraged to turn directly to Part B and make reference to the other material if more detail is desired. The accepted manuscript in the final publication format is included at the end of Part C.

Acknowledgements

Firstly I would like to acknowledge my wife Hanri and my three children Lene, Anina and Lara. They have sacrificed a lot so that I could complete my studies and this research. Thank you for always understanding and supporting me.

Both of my supervisors have played an enormous role in this project.

Dr Leon Du Toit has made this project a success. His dedication and high standards have inspired me and have ensured that the research is of high academic standard.

Prof Ross Hofmeyr has ensured that this project progressed steadily with his knowledge of the processes and his timely contributions. His experience with the scientific process was invaluable.

Tristan Naidoo from the statistics department has gone the extra mile, spent many hours analysing the data, and producing beautiful images that portray the data in an easy-to-understand manner. Tristan your input into the project was very much appreciated.

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Gregg from Augustine Medical. Thank you for all your help and support. You were always available to help with consumables. Your help and time are really appreciated.

Future research

The data collected will be used for a device comparison of the Zero Heat Flux monitor and the oesophageal thermistor. This comparison does not form part of this dissertation but the use of the data for this purpose is mentioned in the protocol.

Table of Contents

Tables and Figures

Tables

Figures

Abbreviations and Scientific Notation

It is anticipated that the reader is familiar with common scientific notation and frequently used medical abbreviations. The terms used in this dissertation are presented below for clarity.

ASA	American Society of Anesthesiologists
BIC	Bayesian information criterion
BMI	Body Mass Index
CI	Confidence interval
CRF	Case report form
HPCSA	Health Professions Counsel of South Africa
HREC	Human Research Ethics Committee
ID	Identity
IQR	Interquartile range
IV	Intravenous
MIN	Minutes
MST	Mean skin temperature
NICE	National Institute for Health and Care Excellence
PI	Principal investigator
SAJAA	Southern African Journal of Anaesthesia and Analgesia
SD	Standard deviation
SGA	Supraglottic airway device
UCT	University of Cape Town
UK	United Kingdom
USA	United States of America
ZHF	Zero heat flux

Part A – Research Protocol

Introduction

Study investigators: Francois Steyn (MMed candidate), Leon du Toit (principal investigator and Supervisor), Ross Hofmyer (Co-supervisor), Asfree Gwanyanya (co-investigator) and Anneli Hardy (Statistician).

Contact details Leon du Toit: 021 404 5001 (during office hours)
Contact details Human research Ethics Committee: 021 650 3002 (during office hours)

This observational study aims to analyse the relationship between preoperative and intraoperative body thermometry readings in consecutive eligible cases of eye surgery under general anaesthesia at Groote Schuur hospital.

Purpose of the study

The study question: In a scenario that limits heat loss to the environment, does skin thermometry prior to induction of anaesthesia predict hypothermia (core temperature < 36 degrees Celsius) under general anaesthesia?

Feasibility

The feasibility study (HREC 772/2018) allowed us to test the method of data collection and build the protocol for the full observational study.

The feasibility study recruited 17 patients over 10 elective theatre days. The average (SD) patient was 50 (18) years old with a BMI of 27 (5) and a median ASA score of 3. The average theatre temperature was 20.8 (0.8) °C. The average duration of anaesthesia was 112 (40) minutes. In 2/17 cases the anaesthesia time was < 60 minutes. We observed an intraoperative hypothermia event rate approaching 50% (8/17). The average preoperative mean body temperature was 35.7 (0.4) °C and core temperature was 36.9 (0.4) °C (by zero-heat flux monitoring; ZHF). The average core temperature at 60 minutes was 36.3 (0.4) °C by oesophageal thermistor (and was no different from the ZHF recording at the same timepoint). No adverse patient outcomes occurred during the feasibility study.

The feasibility study achieved the set objectives allowing us to submit this full proposal.

Background

Perioperative hypothermia contributes to adverse patient outcomes [1,2,3,4], but remains common despite the availability of intraoperative insulation and warming practices [1,2,5,6,7]. Redistribution of body heat is universal after induction of anaesthesia, and is the main contributor to the observed decrease in core temperature [8]. Prewarming patients before induction of anaesthesia reduces the phenomenon of redistribution hypothermia [7,8], but requires additional time, equipment and consumables. The ability to predict which patients are at risk (or which will

benefit from prewarming) can change practice, improve precision care, and avoid unjustified expenditure in the perioperative period.

We ask the question, does preoperative thermometry differ between those who develop intraoperative hypothermia and those who do not?

Methodology

Study design

Prospective observational study of repeated measures of body thermometry in consecutive adult ophthalmic surgery patients at Groote Schuur Hospital.

Characteristics of the study population

All adult patients undergoing elective ophthalmic surgery under general anaesthesia at Groote Schuur Hospital during the study period are eligible for inclusion. The study population is selected because ophthalmic surgery presents negligible physiological insult. Patients are almost completely covered – insulated from environmental factors affecting core temperature change. There is no evidence to support routine active warming of these patients, which would confound observations in other settings.

Recruitment and enrolment

Consecutive patients will be approached at the time of the routine preoperative anaesthetic assessment to obtain informed consent.

Research procedures and data collection methods

The number of eligible patients will be documented during the study. Enrolled participants will have their skin temperature measured at torso, arm, thigh and calf using a commercial surface temperature thermometer preoperatively. Core temperature will be measured continuously using a ZHF monitor (starting preoperatively) and an oesophageal thermistor (starting after induction of anaesthesia). Usual care will proceed with special attention being paid to limiting patient exposure to the environment and to cold intravenous fluids. In theatre the participant will be covered with a forced air warming device that will be used to warm the participant actively if their body temperature decreased to below 36 degrees Celsius. Observations will be documented by an investigator on the attached case report form (CRF).

Data safety and monitoring

Individual patient CRFs will be stapled to one copy of the patient consent form. From the CRFs data will be captured onto a password protected electronic database where only the study generated participant ID number can be used to link the data back to the patient. After data capturing is completed the CRFs with attached patient consent forms will be filed together in the study folder and locked in the archive at the UCT Department of Anaesthesia and Perioperative Medicine. The folder will be kept for 5 years and labelled to be destroyed after 5 years. The cleaned electronic dataset will be uploaded to ZivaHub after publication of the study. The data will be available to other

researchers on request to one of the principle investigator, at the discretion of the principle investigator. At no time will any patient identifiable information be recorded in the electronic database, used in analysis, or published in any form.

The nature of the study does not require data monitoring or interim analyses.

Data analysis

Data will be summarised using mean (standard deviation), median (interquartile range), or frequency (proportion) as appropriate for the data type.

1. Primary outcome: alternative hypothesis: Those who experience intraoperative hypothermia (core temperature < 36.0°C) as measured by oesophageal thermistor have a different (lower) preoperative mean body temperature than those who do not experience preoperative hypothermia. Tested by student's t-test (or Wilcoxon rank sum test).

2. Secondary outcomes: alternative hypotheses:

    a. Those who experience intraoperative hypothermia as measured by ZHF monitor have a different (lower) preoperative core temperature as measured by ZHF monitor. Tested by student's t-test (or Wilcoxon rank sum test).

    b. ZHF monitoring correlates with oesophageal temperature. Tested by linear regression and Pearson's correlation at correlated timepoints.

    c. Preoperative thermometry correlates with intraoperative core temperatures at repeated time points. It is expected that correlation will decrease over time. Tested by Pearson's correlation at repeated time points.

    d. The hazard of intraoperative hypothermia is associated with preoperative thermometry, BMI, and frailty. Tested by time to event / survival method (Cox proportional hazards or appropriate parametric model).

    e. Intraoperative core temperature is associated with preoperative thermometry, BMI and frailty. Tested by repeated measures modelling (mixed effects model).

Primary analysis will be performed in RStudio.

Sample size

The necessary sample size is estimated for the primary outcome. For a t-tests of difference between two independent means, using a two tailed test, an effect size d = 0.81 (based on mean 1: 35.5, mean 2: 35.8, SD: 0.37), a level of significance (α error probability) of 0.05 and power (1-β error probability of 0.8, with an allocation ratio 1:1, total sample size of 50 is required.

The study will use purposive sampling until 25 complete cases have been recorded in the smallest group. A complete case being defined as a patient with core temperature recorded until at least 60 minutes.

From the feasibility study it is anticipated that this will require 5-6 weeks of data collection time.

Description of risks and benefits

This simple observational study poses no known risk or benefit to the participants. This is supported by the absence of adverse patient outcomes during the feasibility study.

No equipment will be purchased for the study.

Informed consent process

Eligible patients will be approached with the consent form (appendix) prior to surgery. The study will be explained and patients will be given opportunity to ask questions. The informed consent form will be signed in triplicate. One copy will be kept in the patient folder, one in the study folder stapled to the individual participant CRF and the other given to the patient.

Privacy and confidentiality

Described above

Reimbursement for participation

None

Emergency care and insurance for research-related injuries

As described in the consent statement

What happens at the end of a study?

The data will be analysed and written up as a manuscript ready for publication. The manuscript will we submitted for publication in a peer-reviewed field-specific journal. The manuscript will also be used as part of the MMed dissertation of Dr Francois Steyn. Data will be stored as described above.

Study Funding and Budget

There are no additional costs related to the study. The commercial skin temperature sensors are owned by the Department of Anaesthesia and Perioperative Medicine and by the Department of Human Biology. The ZHF temperature sensors are sponsored by 3M. 3M has no input in the study design, analysis, write-up or publication of the research. Departmental funding will pay for any statistical support required in the process.

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Part B – Accepted - Publication ready manuscript

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Abstract

Background: Despite numerous guidelines on perioperative temperature management, perioperative hypothermia remains common. Prewarming to prevent redistribution hypothermia is supported by evidence, but not widely practiced. We investigate the measurement of preoperative mean body temperature as a potential tool for individualising the practise of prewarming.

Methods: We hypothesised that patients who experience intraoperative hypothermia have a lower preoperative mean body temperature. A longitudinal study was conducted in adult patients presenting for ophthalmological surgery under general anaesthesia, to describe the relationship between the incidence of hypothermia within the first hour of anaesthesia and preoperative mean body temperature.

Results: Sixty-five patients were enrolled. Twelve participants (18%) presented to the operating theatre hypothermic (core temperature <36.0°C). A further twenty-eight (43%) became hypothermic during the procedure. All hypothermia events occurred within sixty minutes after induction of anaesthesia, and half of the events occurred within nineteen minutes. The difference in preoperative mean body temperature between those with- and without intraoperative hypothermia was only -0.2°C (95% CI -0.4, 0.1). This is neither clinically relevant nor statistically noteworthy. In Cox proportional hazards analysis, BMI and ASA status compounded the observed association between preoperative mean body temperature and the incidence of intraoperative hypothermia. A higher BMI and ASA are associated with a lower incidence of hypothermia.

Conclusion: We conclude that intraoperative hypothermia is common and occurs early after induction of anaesthesia. We observed no useful difference in preoperative mean body temperature to help distinguish between patients who become hypothermic and those who do not. Without a useful risk prediction tool, a generic approach to prewarming remains appropriate. Preoperative screening for pre-existing hypothermia should be practiced, even in cases considered as low risk.

Keywords: inadvertent perioperative hypothermia, redistribution hypothermia, mean body temperature, mean skin temperature

Introduction

Inadvertent perioperative hypothermia is defined as an unplanned core temperature of less than 36°C occurring during the perioperative period.[1, 2] It is associated with numerous adverse patient outcomes[3-5] including increased surgical site infection rates,[4-6] blood loss,[5, 7] length of hospital stay[6] and cost of care.[1, 8-10] Despite the ubiquity of guidelines to prevent perioperative hypothermia, the reported incidence ranges between 20 and 90%.[3, 11]

In the non-anaesthetised person, peripheral thermoregulatory vasoconstriction maintains the core temperature by limiting blood flow to the skin which interfaces with the cold environment. This creates a heat exchange system with a core-to-peripheral temperature gradient, allowing the core temperature to be maintained despite mean body temperature changes.[13, 14]

Mean body temperature is the average temperature of the body. Under normal thermoregulation, peripheral temperature changes to allow either heat conservation or heat loss for the purpose of maintaining a constant core temperature. With heat conservation, the gradient between the core and the skin is high and the mean body temperature is lower compared to a heat loss state, where the gradient between the core and the skin is low and the mean body temperature is higher. Anaesthesia obliterates this mechanism by causing peripheral vasodilatation and lowering the hypothalamic thresholds at which thermoregulatory vasoconstriction and shivering responses are initiated.[15] Redistribution hypothermia will occur even in the presence of intraoperative warming.[16]. The heat gain from intraoperative warming is not enough to prevent the core temperature from decreasing to hypothermic levels due to the pre-existing temperature gradient between the core and the peripheries.[17] During the first thirty minutes of general anaesthesia, close to 90% of the decrease in core temperature is due to redistribution of heat from the core to the periphery. From thirty to sixty minutes, 66% of the ongoing decrease in core temperature is attributable to heat redistribution.[12] In the absence of prewarming, re-establishing normothermia after redistribution can take longer than an hour.[18] Prewarming supplies heat to the peripheries, reducing the core-to-peripheral gradient prior to anaesthesia-induced heat redistribution.[12]

Mechanistically, adverse outcomes are not only related to a single temperature measurement at the end of surgery or on arrival in the postoperative recovery area, but to the duration of hypothermia exposure.[18] Inadvertent hypothermia should be prevented at all times, making prewarming the logical gold standard.

Numerous guidelines are available on perioperative temperature management.[1, 2, 19, 20] Prewarming is commonly recommended. Despite evidence supporting the efficacy of prewarming periods as short as 10 minutes,[21] the practice has not been widely adopted. Poor adoption has been attributed to a lack of buy-in from practitioners,[11] increase in expenses, and lack of knowledge.[11] Some day-case surgery centres claim a low incidence of hypothermia with short procedures and do not want to accrue the extra expense of an active warming device.[22]

In an age of precision medicine, guidelines should strive to be patient specific. Although some guidelines include preoperative hypothermia risk assessment, this does not translate to any specific prewarming recommendations,[1] with the exception that those found to be hypothermic preoperatively be warmed prior to induction of anaesthesia. We seek a more individualised approach to prewarming of surgical patients.

The primary objective of this study was to describe the difference in preoperative mean body temperature between patients who develop intraoperative hypothermia, and those who do not. Secondary aims included testing the effect of measured confounders on the association between preoperative body temperature and intraoperative hypothermia. Risk factors associated with inadvertent hypothermia include, low ambient temperature, large surface area exposure, open body cavities, cold intravenous fluids, extremes of age and low body mass index (BMI).[1] We hypothesised that estimated preoperative mean body temperature predicts the extent of initial core temperature decrease post induction of general anaesthesia, with patients who develop intraoperative hypothermia before sixty minutes having a lower preoperative mean body temperature than those who do not develop intraoperative hypothermia.

Methods

Study design, setting and participants

With approval of the Human Research Ethics Committee of the University of Cape Town (HREC772/2018) and the written informed consent of participants, this study was conducted at a tertiary level hospital in Cape Town, South Africa. We employed a longitudinal study design with repeated measurement of temperature over time. We used consecutive sampling of adult patients presenting for elective ophthalmic surgery requiring general anaesthesia, where the surgery had an expected duration of at least an hour. Ophthalmic surgery was selected due to minimal environmental exposure of the patients, and the lack of blood loss and fluid shifts.

This was done as a method for restricting these known confounding factors from biasing the observed effect of heat redistribution after induction of general anaesthesia.

Patients were deemed eligible if they were 18 years or older. Patients with a recent fever or known sepsis were excluded. Recruitment and informed consent took place in the ward, typically on the day prior to surgery.

Variables and methods of measurement

The primary outcome was preoperative mean body temperature. Secondary outcomes were preoperative mean skin temperature and Zero heat flux (ZHF) temperature. Mean skin temperature is the average temperature of the skin. Different skin regions have different temperatures which are related to blood flow and adipose distribution. In this study the mean skin temperature was calculated using the Ramanathan method.[24] ZHF temperature is a non-invasive core temperature measurement. It consists of a sensor placed on the forehead which creates a zone of insulation that eliminates heat loss to the environment. An isothermic pathway is formed which allows core temperature to be measured at the skin surface.[38]

Baseline variables were collected in the ward during the recruitment visit, and in the induction room of the operating theatre prior to anaesthesia. Skin temperature was measured in the induction room, using a handheld thermocouple thermometer with a surface probe (Thermapen™, Electronic temperature instruments Ltd., West Sussex, United Kingdom). Operating room temperature and core temperature according to a ZHF monitor (3M™ SpotOn™, St. Paul, Minnesota, USA) were recorded immediately prior to induction. Thereafter, from the time the participant was connected to monitoring in the operating theatre until the time of tracheal extubation, body core temperature was measured continuously using the ZHF monitor. Body core temperature was also measured with a thermistor placed in the mid-oesophagus or nasopharynx which was placed with intubation. After induction of general anaesthesia, the patient's core temperature was documented every 15 minutes. The time-to-hypothermia interval was recorded in 1-minute increments. Data collection procedures during the study as well as the body sites and calculation used are described in Figure 1.

Other recorded baseline variables were patient demographics: ASA status, Edmonton frailty scale,[23] sex, age, BMI, and case related variables: airway management (endotracheal tube or supraglottic airway), volume of intravenous fluid administered during the procedure, and

duration of the procedure from induction of anaesthesia to emergence. All fluids were warmed preoperatively in a fluid warmer set at 40℃.

Four pre-identified body sites based on the Ramanathan method,[24] were used to calculate mean skin temperature.[25] Mean body temperature was calculated using a weighted formula involving both the mean skin temperature and the core temperature, (Figure 1).[24] The thermometer used for skin temperature measurements has an accuracy of 0.4°C, within the range of -49.9°C to 299.9°C. During and after these measurements, the patient was covered as much as possible with a cotton blanket to prevent heat loss. The temperature sensor was applied to the skin for two minutes to allow equilibration of each reading. The ZHF sensor was attached to the forehead above the non-operative eye. The ZHF sensor has an accuracy of 0.23°C.

The choice of anaesthetic technique and agents was left to the discretion of the attending anaesthesiologist. After endotracheal intubation, an oesophageal thermistor was placed orally at 20 cm from the teeth. The thermistor has a range of 25-45°C and an accuracy of 0.1°C. In cases where a supraglottic airway was used, the thermistor was placed in the nasopharynx. Intravenous fluids were limited to as little as necessary, and the volumes were recorded at the end of the case.

A forced-air warming blanket was placed over each patient but not switched on. Active warming of the patient was initiated if the core temperature dropped below 36°C. At this point, the time to hypothermia was documented, and temperatures recorded subsequently were excluded from analysis.

Classification of hypothermia was based on oesophageal temperature, except when a supraglottic airway was used, in which case the ZHF temperature was considered a more accurate method of determination. During pilot data collection it was observed that the thermistor placed in the nasopharyngeal position in the presence of a supraglottic airway device frequently produced spurious readings. Oesophageal readings were favoured over the ZHF readings as it is a more widely used modality and its accuracy is well established. When oesophageal temperature readings were recorded below 36.0 degrees from the start of the case (baseline), the case was classified as preoperative hypothermia (left censored) and excluded from the primary analysis.

Study size

The incidence of hypothermia was unknown in this population, and no previous studies pertaining to the correlation between preoperative mean body temperature and perioperative hypothermia could be found. Therefore, a pilot study was conducted to inform our sample size calculation. The pilot study was conducted over 10 consecutive theatre days (11 February to 2 March 2019). Seventeen patients were investigated, of whom eight (47 %) became hypothermic.

We used the pilot study data to estimate the required sample size for a two-sample t-test. Given an effect size of 0.3°C difference in mean body temperature between groups (SD 0.37), to obtain power of 0.8 at a two-sided level of significance of 0.05, required a sample size of 50 patients with a ratio of 1:1. Based on this estimate it was determined *a priori* that recruitment would be continued until the smallest comparison group (with or without an incident of hypothermia) included 25 participants.

Statistical method

Baseline and outcome variables were described using summary statistics; mean (SD) for continuous variables, median (interquartile range) for ordinal variables and count (percentage) for categorical variables.

The primary objective (difference in preoperative mean body temperature between those who develop hypothermia in the first 60 minutes of anaesthesia compared to those who do not) and secondary objectives (difference in preoperative mean skin temperature and ZHF temperature between those who develop hypothermia in the first 60 minutes of anaesthesia compared to those who do not) were assessed using a two sample t-test.

A survival analysis using Kaplan-Meier estimation and Cox proportional hazards analysis was conducted to explore effects of all measured variables on the experience of hypothermia and the association between preoperative mean body temperature and hypothermia. Model building used the likelihood ratio test and Bayesian information criterion (BIC) in sequential models with increasing number of variables and first order interactions to identify the model that best fits the data. Proportional hazards, overall fit, outliers, influential observations and functional form of variables were assessed in model diagnostics.

Statistical analysis was conducted with R (R Core Team, 2020. R Foundation for Statistical Computing, Vienna, Austria). The survival analysis made use of the 'survival'[26] and 'survminer'[27] packages. This manuscript was prepared in accordance with the STROBE statement.[28]

Results

Participants

Of the patients approached during recruitment, three did not consent and were not enrolled. A total of 65 participants were enrolled in the study during the period from 24 June until 1 August 2019.

Mean participant age and BMI were 49 years and 26.1 $kg.m^{-2}$ respectively. 54% (35/65) of the participants were female. Median ASA grade was 2. Table 1 reports additional details of participant and case characteristics.

Missing data: One participant's oesophageal temperature sensor produced non physiological readings; for this case data from the ZHF sensor was substituted for analysis. Data for calculating BMI was not recorded in 4 participants, IV fluid administered was not recorded for 8 participants and the room temperature was not recorded for 4 participants.

Outcome data

Of the 65 enrolled participants, twelve (18.5%) were hypothermic at baseline, twenty-eight (43%) became hypothermic after induction of anaesthesia, and only twenty-five (38.5%) did not experience hypothermia. (Table II). The difference (95% confidence interval) in preoperative mean body temperature between those who developed hypothermia after induction of anaesthesia and those who did not was -0.2°C (-0.4, 0.1). (Figure 2). The differences in ZHF temperature and mean skin temperature were -0.1°C (-0.4, 0.1) and -0.2 (-0.7, 0.3).

Further analysis of the change in core temperature over time using a Kaplan-Meier estimate demonstrated median time (95% CI) to hypothermia as 19 (13, 23) minutes after induction of anaesthesia (Figure 3). Hypothermia events occurred early after induction of anaesthesia :86% (24 of 28 events) occurred within 30 minutes and no events occurred after the first hour.

The results of the Cox proportional hazards analysis are summarised in Table 3. Of the variables considered for inclusion in the model – preoperative mean body temperature, age, ASA, BMI, Edmonton frailty score, room temperature and volume of IV fluid infused – only preoperative mean body temperature, BMI and ASA were included in the final model as the other variables were not independently associated with the development of hypothermia or did not improve the model when comparing sequential models. Inclusion of first-order interactions did not improve the model and were not included in the final model reported here.

The relationship between BMI and hypothermia is demonstrated in the Supplemental Figure – the hazard of hypothermia was lower in those with a higher BMI and higher in those with a lower BMI (p=0.002; log-rank test).

Discussion

Key results

There was no statistically notable, nor clinically relevant difference in the preoperative mean body temperature between the group who became hypothermic and the group who remained normothermic (mean [SD] 35.3 [0.5]°C and 35.4 [0.4]°C respectively). The same held true for preoperative mean skin temperature and preoperative core body temperature. Even in our relatively healthy study population of patients with nearly no body surface exposure, inadvertent perioperative hypothermia was very common (a prevalence of 62%), with an incidence of hypothermia after induction of anaesthesia of 43%.

Limitations

The study was conducted at only one institution. By design, the observed decrease in core temperature is believed to be mainly representative of redistribution hypothermia. However, the amount of heat loss to the environment was not measured. Our outcome of primary interest was preoperative mean body temperature, but there was no practical way to measure this directly in our study. Our calculation of this variable, although previously validated, could be a source of measurement error. Our data cannot be used to estimate the drop in core temperature in other types of surgery, as the amount of heat loss will be significantly higher in surgeries with more surface exposure. Although the number of enrolled participants were sufficient to address our primary objective, it remains too small to adequately explore other predictors of

redistribution hypothermia. Our time-to-event analysis suggest the importance of BMI and possibly ASA status as predictors, but other measured variables cannot be excluded as determinants due to the limited sample size and restricted observed ranges of participant characteristics.

Interpretation

The high incidence of inadvertent perioperative hypothermia in our study is in keeping with findings of other researchers such as Moola *et al*, Inal *et al* and Sun *et al*.[3, 11, 18] We demonstrate this to be true even in surgery that is considered low risk, where exposure is limited, and there is minimal blood loss. The importance of preoperative screening for hypothermia has been highlighted in this study, with 19% of patients arriving to theatre hypothermic. This supports the guidance of the National Institute of Health and Care (NICE) in the UK, which states that patients should be screened preoperatively in the ward and should not be allowed to go to the operating theatre if they are hypothermic, but should instead be actively warmed until they are normothermic (except in the case of an emergency).[1]

Our study demonstrates a limitation in the understanding of redistribution hypothermia. Prewarming increases peripheral heat content and therefore decreases the core to peripheral gradient. This mechanism has repeatedly been shown to prevent redistribution hypothermia.[3, 4, 9, 11, 17, 20] Our failure to demonstrate a relationship between the mean preoperative body temperature, the mean skin temperature and the core temperature to the incidence of redistribution hypothermia suggests that other important determinants exist and are commonly at play or that these measures are not a true reflection of the core to peripheral gradient

The observed short time to development of hypothermia is noteworthy. Redistribution of heat occurs rapidly, with most of the observed events in our study occurring within 30 minutes following induction of anaesthesia. Literature typically reports the incidence of hypothermia in the first hour of anaesthesia[18, 29] or the absolute core temperature decrease in the first hour[14, 30] rather than time to hypothermia.

Short procedures should not be seen as low risk for hypothermia. No hypothermic events occurred after an hour of anaesthesia, which suggests that redistribution takes less than an hour. It also suggests that the study was successful in observing only redistribution as a reason for decrease in core temperature. Other literature reports hypothermic events after an hour.[14, 18, 29]

These studies, however, include surgeries where ongoing heat losses played a role. In these studies, the rate of temperature decrease changes at about one hour, which is further evidence that redistribution is complete at this time and that continued decrease in temperature is due to ongoing heat loss to the environment.[14, 18]

Further exploration of our data using time-to-event analysis generated hypotheses about other determinants of redistribution hypothermia. Although preoperative mean body temperature was not predictive of hypothermia when assessed across the whole study sample, a lower BMI was a notable risk factor for development of hypothermia, while a higher BMI appears to have been protective. The observed data fits the hypothesis that preoperative mean body temperature becomes an important determinant of the intraoperative development of hypothermia in those with a lower BMI. This observation is in keeping with the research of Ozer *et al* and Fernandes *et al*.[31, 32]

An association with unexpected direction was observed between ASA status and the development of hypothermia, whereby those with an ASA status of 3 experienced a lower hazard of hypothermia compared to those with an ASA status of either 1 or 2. This unexpected association may be spurious, due to the relatively small dataset and restricted spectrum of participants, and interrater variability in ASA classification. The association did not appear to be solely explained by any association between BMI and ASA status. Numerous studies have looked at the relationship between ASA status and the development of perioperative hypothermia. The results are incongruent, with some studies demonstrating that ASA has an impact on the development of hypothermia[33-35] while other studies found no such correlation.[36, 37] We are not aware of any studies that show a protective element with higher ASA scores. One reason for a true discrepancy may be that our design effectively studied heat redistribution, while in other studies, heat loss to the environment is the dominant determinant of body temperature.

In conclusion, inadvertent perioperative hypothermia is common, even in low risk patients and low risk procedures. Our findings underpin the importance of screening for preoperative hypothermia as described in the current NICE guidelines.[1] Hypothermia resulting from heat redistribution occurs early after induction of anaesthesia (within the first hour), so that prewarming (even for short procedures) should strongly be considered. Future work should explore BMI and ASA status along with other determinants of hypothermia, striving towards

a patient-specific approach to perioperative warming that is informed by a better understanding of perioperative thermal physiology.

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Table 1: Participant and case characteristics reported as mean (SD) for continuous variable, median (IQR) for ordinal variables, and frequency (proportion) for dichotomous variables.

	Hypothermia at baseline (n=12)	Hypothermia during anaesthesia (n=28)	No hypothermia observed (n=25)
Age (years)	49.8 (14.8)	46.0 (17.1)	52.5 (15.9)
Body mass index (BMI)[θ]	26.0 (3.6)	24.0 (4.2)	28.4 (4.7)
Sex: Female	6/12 (0.50)	15/28 (0.54)	14/25 (0.56)
ASA status*	2 (2, 3)	2 (1, 2)	3 (2, 3)
Edmonton frailty score‡	2 (1, 4)	3 (2, 5)	3 (2, 4)
Duration of anaesthesia (min)	97 (24)	110 (45)	107 (38)
IV fluid volume (l)[Δ]	0.883 (0.252)	0.743 (0.306)	0.684 (0.279)
Room temperature (°C)[φ]	21.2 (1.1)	20.5 (1.1)	20.8 (1.3)
SGA (cp. Endotracheal tube)	1/12 (0.08)	4/28 (0.14)	2/25 (0.08)

* Maximum observed ASA status = 3. ‡ Maximum observed frailty score = 8. ASA is American Society of Anesthesiologists Physical Status Classification. IV is intravenous. SGA is Supraglotic airway device. [θ] BMI data was missing for 1 and 3 participants in the 'hypothermic before anaesthesia' and 'hypothermia during anaesthesia' groups. [Δ] IV fluid volume was not recorded for 1, 4 and 3 participants in the groups 'hypothermic before anaesthesia', 'hypothermia during anaesthesia' and 'no hypothermia'. [φ] Room temperature was not recorded for 3 and 1 participants in the 'hypothermia during anaesthesia' and 'no hypothermia' groups.

Table 2: Preoperative body thermometry, mean (SD), grouped by participant experience of hypothermia during the first 60 minutes of anaesthesia.

	Hypothermia at baseline (n=12)	Hypothermia during anaesthesia (n=28)	No hypothermia observed (n=25)
Preoperative ZHF temperature (°C)	36.2 (0.8)	36.8 (0.5)	36.9 (0.4)
Preoperative mean skin temperature (°C)	32.8 (0.8)	32.6 (0.9)	32.8 (0.9)
Preoperative mean body temperature (°C)	34.7 (0.6)	35.3 (0.5)	35.4 (0.4)

ZHF is the zero heat flux forehead reading.

Table 3: Final multivariable Cox proportional hazard model

	HR	95% CI	p-value
Preoperative mean body temperature (°C)	0.23	0.07-0.77	0.017
Body mass index (BMI)	0.83	0.74-0.94	0.002
ASA (reference: 1)			
ASA: 2	0.71	0.29-1.77	0.467
ASA: 3	0.19	0.06-0.62	0.006

Figures

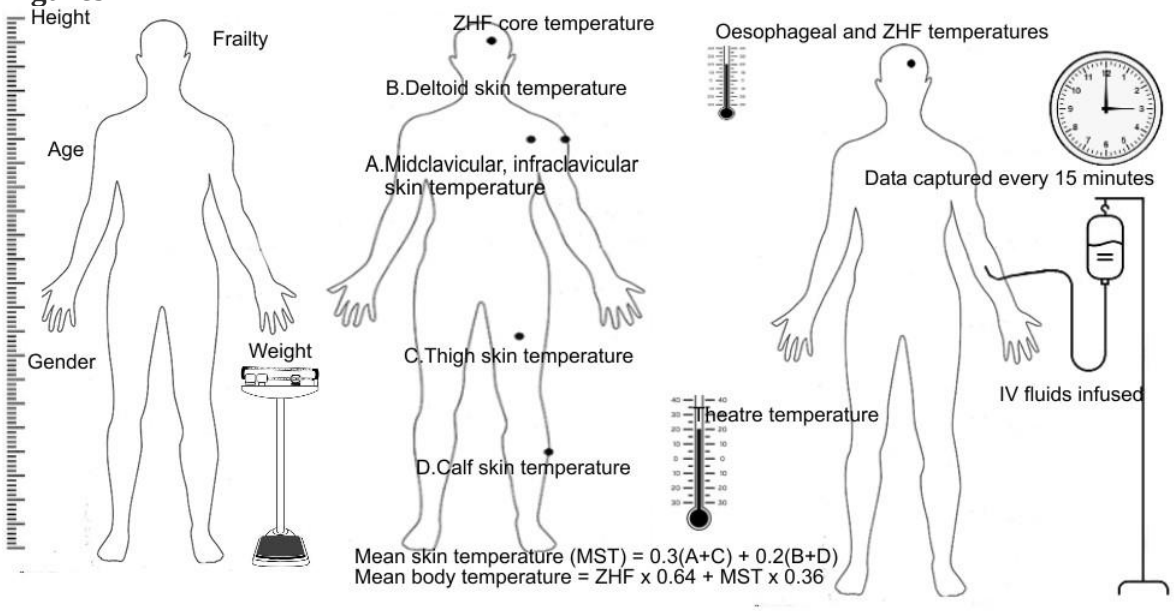


Figure 1: Measured variables. Zero heat flux (ZHF), intravenous (IV)

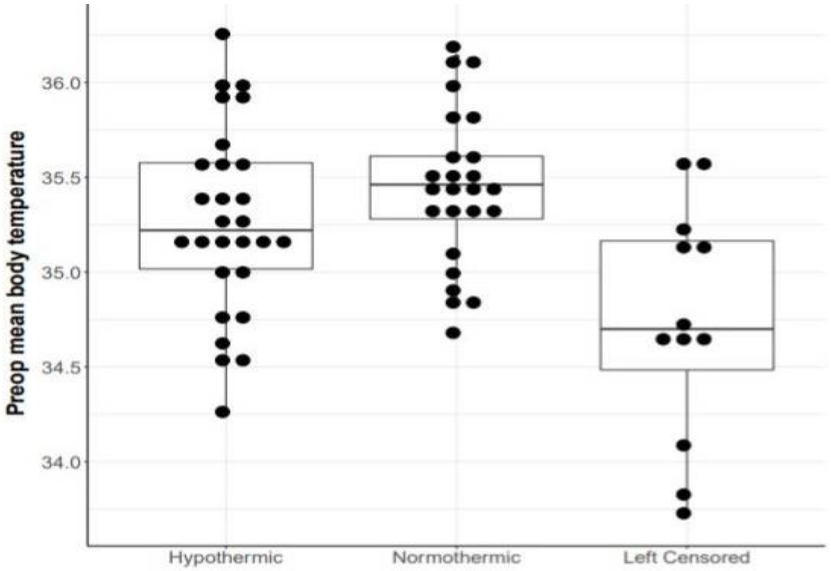


Figure 2: Box and dot plot of preoperative mean body temperature distribution by core temperature outcome during the first 60 minutes of anaesthesia. Left censored data are those participants who were hypothermic at baseline and therefore excluded from the primary outcome.

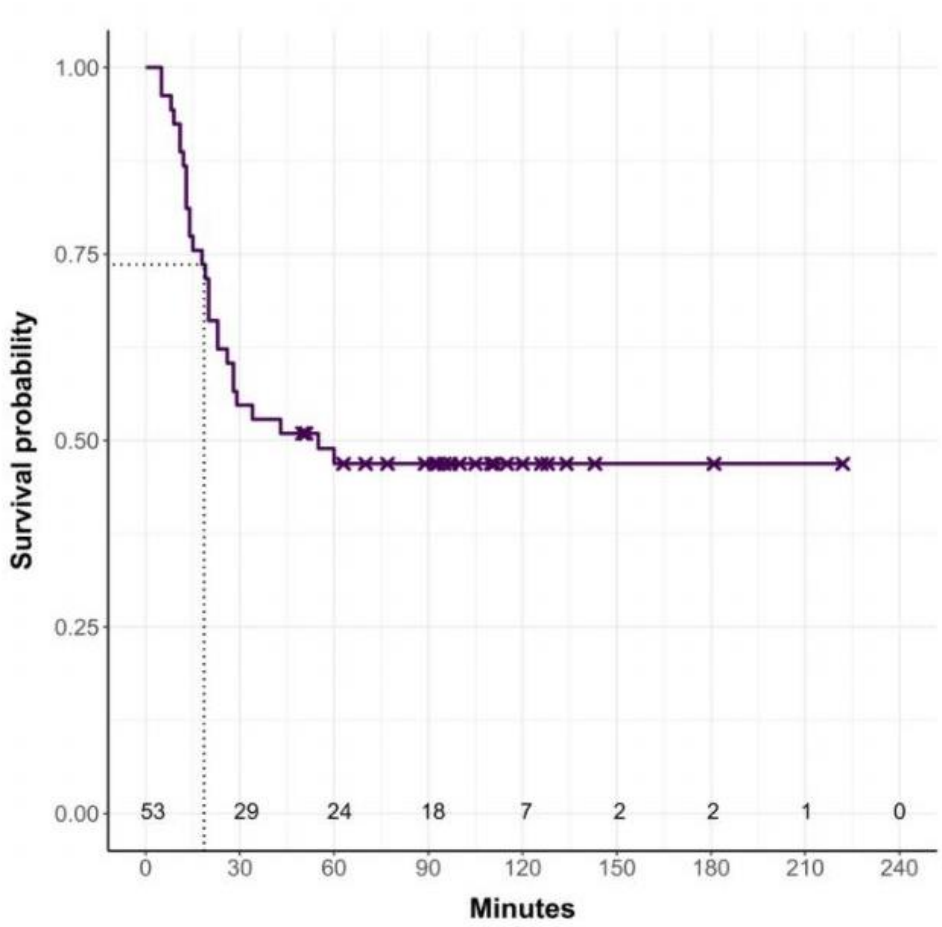
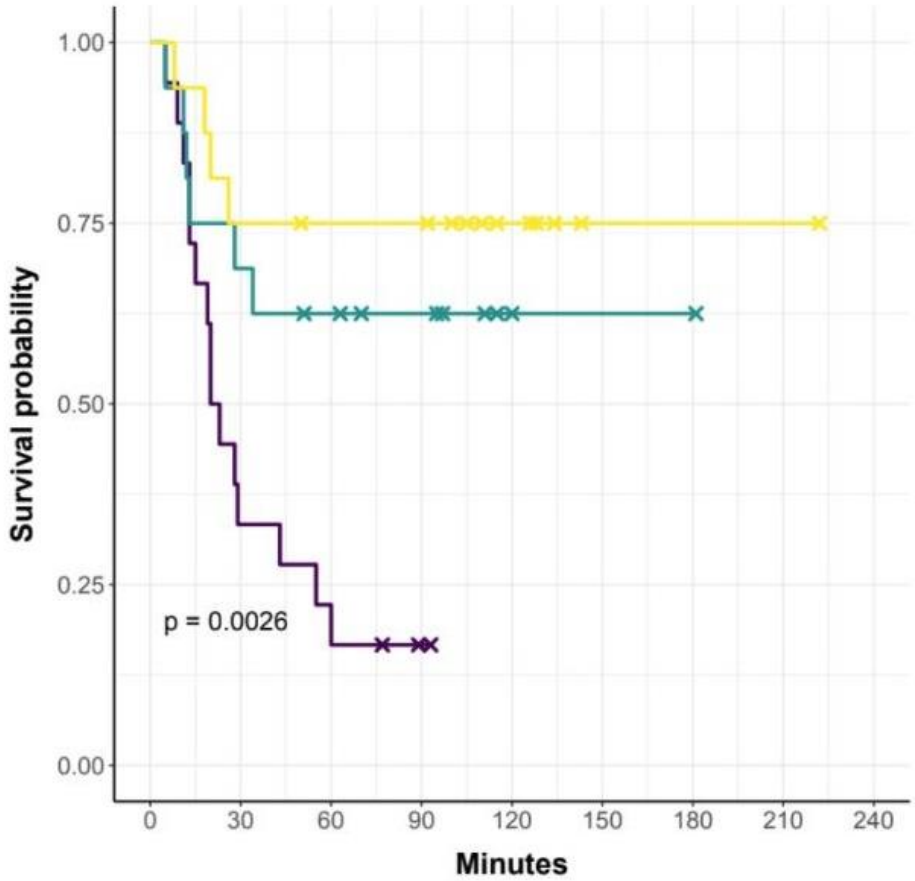


Figure 3: Kaplan-Meier plot of time to hypothermia in patients with starting core temperature greater than 36.0 °C. Median time to hypothermia is 19 minutes. Number at risk indicated at bottom of plot area along with corresponding time in minutes. Censoring events indicated with a 'x'. Survival probability on the y-axis is the cumulative probability of NOT developing intraoperative hypothermia.



Supplemental Figure 4: Kaplan-Meier plot of the probability of not experiencing hypothermia stratified by tertiles of body mass index (BMI) with p-value for the log-rank test. Upper yellow tertile (27; 39], middle teal tertile (23; 27], lower purple tertile [18; 23]. Survival probability on the y-axis is the cumulative probability of NOT developing intraoperative hypothermia.

Part C: Supplementary and supporting documents

Informed Consent Form

A feasibility study measuring body temperature before and during eye surgery.

Study investigators: Francois Steyn (MMed candidate), Leon du Toit (principle investigator and co-Supervisor), Ross Hofmeyr (Co-supervisor), Asfree Gwanyanya (co-investigator) and Anneli Hardy (Statistician).

Department of Anaesthesia and Perioperative Medicine, University of Cape Town, South Africa

INFORMATION

It is common for body temperature to decrease during surgery and anaesthesia. When it decreases below 36°C patients may develop more complications after surgery. These complications include increased blood loss, increased infections and a longer stay in hospital. It is also very uncomfortable for patients to wake up cold and to shiver.

This study will help doctors to predict which patients will become significantly cold under anaesthesia. The knowledge may help us prevent the decrease in temperature and its associated complications.

If you choose to help with this study an anaesthetic doctor will make a note of your body temperature before and during anaesthesia. You will only be aware of the temperature measurements that are taken from your leg, arm, forehead and chest while awake. Information about your health and your surgery will be recorded along with your temperature.

If your body temperature decreases below 36 degrees Celsius, we will ensure that you are warmed up during the surgery.

Participating in the study is purely voluntary. Your participation does not affect your surgery or anaesthesia.

The results of the study may improve future patient care. You will not be paid to take part in this study. At no point will your identity be connected to the published data. Your identity will be kept confidential throughout the process.

The investigators have received permission for this research from the Human Research Ethics Committee (HREC no:772/2018). If you have any concerns or questions regarding the study you can contact the researchers directly on 021 404 5001. If you have any ethical concerns you can contact the Human Ethics Research Committee on 021 406 6338.

Please read this form carefully and ask the investigator (study doctor) to explain any words or information that are not clear to you. This will help to ensure you understand the details of your participation before you give your consent. You will be given a copy of this consent form to take home with you. The doctors will answer any questions you may have about this consent form and about the study

CONSENT STATEMENT

I certify that

- I have read and understand what the study is about and what my involvement entails.
- I understand that the doctors will make a copy of some of my routinely recorded data from my standard patient care.
- I have had the opportunity to ask questions. All my questions have been answered to my satisfaction.
- I understand that my identity is kept confidential in this study.
- I have received a copy of UCT's no-faults insurance policy.

_____YES _____NO

_____ _____ dd.mm.yyyy

Participant/Legal Representative's name (printed) **Signature** **Date:**

_____ _____ dd.mm.yyyy

Name of person obtaining consent (printed) **Signature** **Date:**

Study CRF

Sex M ☐ F ☐ Age ☐☐☐ ASA 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ BMI ☐☐

Edmonton Frailty Score ☐☐

			0		1		2
Cognition	Clock drawing	No errors		Minor spacing errors		Other errors	
Health status	Number of hospital admissions in last year	0		1		>1	
	Patient description of overall health	Good		Fair		Poor	
Functional dependence	Help needed with number of ADL	0-1		2-4		5-8	
Social support	Reliable support available	Always		Sometimes		Never	
Medication used	>4 regular medications?	No		Yes			
Nutrition	Recent weight loss	No		Yes			
Mood	Often sad or depressed	No		Yes			
Continence	Urinary incontinence present	No		Yes			
Functional performance	Timed up and go	0-10s		11-20s		>20s	

Preoperative temperature measurements

ZHF ☐☐ , ☐ Arm ☐☐ , ☐ Torso ☐☐ , ☐ Thigh ☐☐ , ☐ Calf ☐☐ , ☐

Intraoperative measurements Theatre temp

ZHF temperature at 15 minute time intervals

15 ☐☐ , ☐ 30 ☐☐ , ☐ 45 ☐☐ , ☐ 60 ☐☐ , ☐ 75 ☐☐ , ☐ 90 ☐☐ , ☐

Oesophageal temperature at 15 minute time intervals

15 ☐☐ , ☐ 30 ☐☐ , ☐ 45 ☐☐ , ☐ 60 ☐☐ , ☐ 75 ☐☐ , ☐ 90 ☐☐ , ☐

Time in minutes to reach 35.9 ☐☐☐

Time from intubation to extubation ☐☐☐

Pilot study protocol

Introduction

Study investigators: Francois Steyn (MMed candidate), Leon du Toit (principle investigator and co-Supervisor), Ross Hofmeyr (Co-supervisor), Asfree Gwanyanya (co-investigator) and Reshma Kassanjee (Statistician).

Contact details Leon du Toit: 021 404 5001 (during office hours)
Contact details Human research Ethics Committee: 021 650 3002 (during office hours)

This is a feasibility study of the utility of body thermometry in predicting hypothermia in consecutive cases of eye surgery under general anaesthesia at Groote Schuur hospital.

Purpose of the study

A feasibility study to determine the required sample size and appropriate statistical plan for answering the study question: In a scenario that limits heat loss to the environment, does skin thermometry prior to induction of anaesthesia predict hypothermia (core temperature < 36 degrees Celsius) under general anaesthesia.

We can find no report in literature of this question being asked previously. We find no documentation of the event rate in the population of interest. It is the investigators' opinion that the event rate may be higher than 50%.
From the observations made in the feasibility study the investigators want to understand:

- How many cases can be recruited during a 4-6 week period.
- What is the event rate in the study population? How many patients develop a core temperature < 36 degrees Celsius within 1 hour of anaesthesia.
- What is the estimated mean skin temperature and mean body temperature of the patients prior to induction of anaesthesia based on simple skin temperature measurement and the first core temperature measurement after induction of anaesthesia.

- Identify practical problems in the data collection process that can be addressed in the main study protocol.

Background

Perioperative hypothermia contributes to adverse patient outcomes [1,2,3,4], but remains common despite the availability of intraoperative insulation and warming practices [1,2,5,6,7]. Redistribution of body heat is universal after induction of anaesthesia, and is the main contributor to the

observed decrease in core temperature [8]. Prewarming patients before induction of anaesthesia reduces the phenomenon of redistribution hypothermia [7,8], but requires additional time, equipment and consumables. The ability to predict which patients are at risk (or which will benefit from prewarming) can change practice, improve precision care, and avoid unjustified expenditure in the perioperative period.

Methodology

Study design

A planned feasibility study in the form of two-week cross-section of the proposed study population.

Characteristics of the study population

All adult patients undergoing elective eye surgery under general anaesthesia at Groote Schuur Hospital during the period of the feasibility study. The study population is selected because eye surgery presents negligible physiological insult. Patients are almost completely covered; insulated from environmental factors affecting core temperature change. There is no evidence to support routine active warming of these patients, which would confound observations in other settings.

Recruitment and enrolment

Consecutive patients will be approached at the time of the routine preoperative anaesthetic assessment to obtain informed consent.

Research procedures and data collection methods

We will screen the eligible population with the intention of enrolling all eligible patients in the two week period. Enrolled participants will have their skin temperature measured from their torso, arm, thigh and calve using a commercial surface temperature thermometer preoperatively. The core temperature will also be measure preoperatively with a zero heat flux monitor. Usual care will proceed with special attention being paid to limiting patient exposure to the environment and to cold intravenous fluids. The participant will be covered with a forced air warming device that will be used to warm the participant actively if their body temperature decreased to below 36 degrees Celsius. Observations will be documented by an investigator on a single feasibility study data collection sheet.

Data safety and monitoring

Included participants will be given a computer generated random participant ID number between 0-40. (We expect that fewer than 40 cases will undergo surgery during a 2week period.) All data will be recorded in a single feasibility study data form

according to the random participant ID number. Data from the feasibility study will be captured onto a single Excel spread sheet that will be stored in a password protected Dropbox folder that only the investigators have access to. There will be no record connecting the participant ID or information to a specific person. The nature of the feasibility study does not require monitoring or interim analyses.

Data analysis

The observations will be used to calculate:

1. How many participants can be studied per week? (Meet inclusion criteria.)
2. How many participants have a starting core temperature lower than or equal to 36 degrees Celsius? (Meet exclusion criteria.)
3. How many participants have a core temperature lower than or equal to 36 degrees Celsius at 1 hour? (Estimated event rate.)
4. What is the average skin temperature and body temperature before induction of anaesthesia?
5. With the amount of data we can gather during the 2 week study period, what would be the best statistical plan be for the primary outcome and which secondary analyses should we plan for?

Description of risks and benefits

This simple observational study poses no known risk or benefit to the participants. No equipment will be purchased for the feasibility study.

Informed consent process

Eligible patients will be approached with the consent form (appendix) prior to surgery. The study will be explained and patients will be given opportunity to ask questions. The informed consent form will be signed in duplicate. One copy will be kept in the patient folder and the other given to the patient. An electronic copy will be kept in the secured study dropbox folder.

Privacy and confidentiality

Described above

Reimbursement for participation

None

Emergency care and insurance for research-related injuries

As described in the consent statement

What happens at the end of a study?

Analysis will inform design of the main study. This is a purely cross-sectional study with no participant follow-up.

Study Funding and Budget

There are no additional costs related to the study. The commercial skin temperature sensors are owned by the Department of Anaesthesia and Perioperative Medicine and by the Department of Human Biology. The zero heat flux temperature sensors are sponsored by 3M. 3M had no input into study design, the conduction of the study, data analysis or the final writeup of the study.

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Form FHS013: New protocol application form – Section A

1. Protocol information

Protocol title	Pilot study: Incidence of inadvertent perioperative hypothermia and the use of body thermometry to predict perioperative hypothermia in ophthalmology patients.

Is this a sub-study or an extension study linked to an existing/main study previously approved by this Committee? (e.g. a sub-study, follow-up study, earlier phase trial) (tick √)	☐ * Yes		☐ No X	
If yes above, please provide the following with regards to the existing/main study:	HREC ref. no.		Expiry approval date of existing/main study	
* Please comment briefly on safety and efficacy findings of the existing/main study that may have relevance to this application. (Please also add a brief description in new study synopsis)				

2. Investigator(s) profile

Note:

- For all postgraduate student research the **main** supervisor must be listed as PI on this form.
- For all undergraduate student research please **only** complete the FHS021 form and not this form.
- The PI or Co-PI **must** be a UCT affiliated person.

2.1 UCT's principal investigator (PI)

Title, first name, surname	Dr Leon Du Toit			
Department/Division	Anaesthesia			
Phone	0845757330			
Email address	Leon.alive@gmail.com			
Department /Office Internal Mail Address for Correspondence				
Registration with HPCSA (tick ✓)	☐√ Yes	☐ No	Registration #	MP0637858
Is the PI covered by professional liability insurance? (tick ✓)	☐ Yes√	☐ No		
If yes above, please provide the liability insurance number.	MED22649POL-18			

Note: If a non-medically trained PI is overseeing research that involves medical procedures, the application must include a medical doctor registered with the HPCSA as a co-investigator.

2.2 Co-investigator(s) Note: Staff and students involved in the research must be listed as co-investigators

Title, first name, surname	Department/Division	Email
Dr Francois Steyn	Anaesthesia	fcoissteyn@gmail.com
Dr Ross Hofmeyr	Anaesthesia	Ross.hofmeyr@uct.ac.za
Mr Asfree Gwanyanya	Human Biology	Asfree.gwanyanya@uct.ac.za
Mrs Reshma Kassanjee	Statistics	Reshma.kassanjee@uct.ac.za

2.3 Is this protocol for degree purposes? (tick ✓)	
☐ Yes√	☐ No
If yes, please specify:	
Type of degree	MMED (FCA)
Student's title, first name, surname	Dr Francois Steyn
Student's email	fcoissteyn@gmail.com

2.4 Supervisor(s)		
Title, first name, surname	Department and University	Email
Dr Ross Hofmeyr	Anaesthesia (UCT)	Ross.hofmeyr@uct.ac.za

2.5 How many of the following does the PI or supervisor currently oversee? (Total number for all research projects)			
Open research studies	0	Sites (excluding this application)	0
Co-investigators	0	Number of participants	0

2.6 What is the PI's role in authoring this protocol? (tick ✓ all relevant)	
Primary author	
Collaborator	√
Supervisor	√
None (developed by sponsors)	

2.7 Are there any publication restrictions on the research?	
☐ Yes	☐ No√
If yes, please describe and justify:	

2.8 Does the protocol comply with UCT's intellectual property rights policy? (tick ✓)	
☐ Yes√	☐ No

3. Protocol profile

3.1 Has this protocol been submitted to another Human Research Ethics Committee? (tick ✓)	
☐ Yes	☐ No√

3.2 To your knowledge, has this protocol been rejected by another HREC? (tick ✓)		
☐ Yes	☐ No√	☐ Don't know

3.3 Is there any vulnerability associated with the proposed participant groups? **Note:** Group vulnerability refers to any potential vulnerabilities relating to pre-existing physiological or health conditions; cognitive or emotional factors; and socio-economic or legal status.		
☐ Low√	☐ Medium	☐ High
Please explain the group vulnerability and justify the need for research in this group of participants.		
The study group are patients coming for eye surgery so often their eye sight is limited. They often suffer from diabetes and hypertension and tend to be elderly. This group was chosen due to the surgical conditions and not due to patient parameters.		

3.4 Please specify the level of risk associated with the proposed research.

Note: Research risk refers to the probability and magnitude of harms participants may experience as a result of the proposed research methods and/or type of data to be collected. Examples include research procedures or collection of data relating to clinical diagnoses or side effects; cognitive or emotional factors such as stress or anxiety during data collection; and socio-economic or legal consequences of research such as stigma, loss of employment, deportation, or criminal investigation.

☐ Low√	☐ Medium	☐ High

Please explain the research risk and justify the need for the proposed research.

Standard of care will be given to these patients except for non routine use of non invasive skin temperature measurements.

3.5 Is this study suitable for an expedited review? I.e. is the research considered to be minimal risk? (tick ✓)

☐ Yes√	☐ No

If yes, please provide a motivation for expedited review:

Standard of care will be provided to patients except for non invasive skin temperature measurements which carries no known risk.

Note: AT THE DISCRETION OF THE HREC CHAIRPERSON OR DESIGNATE, STUDIES REQUESTING EXPEDITED REVIEW MAY NEED TO BE CONSIDERED AT A FULL COMMITTEE MEETING

3.6 Are there additional requirements by a funder or sponsor that require the study to undergo Full Committee review? (tick ✓)

☐ Yes	☐ No√

3.7 Does this protocol comply with all the principles of the Helsinki Declaration of 2013, including care after research, if applicable? (tick ✓)	
☐ Yes√	☐ No

3.8 Is this a protocol for which insurance for research-related bodily injury would be appropriate? (tick✓)	
☐ Yes	☐ No√ (If 'no', please complete 3.8.4 below)

3.8.4 If no insurance for research-related bodily injury is required, please justify by indicating the type/nature of the proposed research:
☐ Qualitative research study
☐√ Purely observational study
☐ Patient folder or document review only
☐ Questionnaires/Interviews only
☐ Study involves secondary data analysis only
☐ No human participants involved in the research study
☐ Other
If other, please specify:

4. Funding and grant information (Required)

Note: A summary budget must be attached in the appendices

4.1 Funding source	**(tick ✓ at least one)**	**Ethics Review Levy – cost including vat**
UCT (e.g. departmental funding / student research)	√	R0
Grant Funding Organizations (e.g. MRC, NRF, CANSA,)		R0
Federally funded / Foundation sponsored / Private Institutions (**BELOW R1m**)		R6 099
Federally funded / Foundation sponsored / Private Institutions (**ABOVE R1m**)		R12 198
Pharmaceutical / Industry Driven company sponsors an investigator to conduct a new research project into Traditional or Complementary Medicine or Nutriceuticals		R12 198
Pharmaceutical / Industry Driven company sponsors an investigator to conduct a new research project		R24 396
Pharmaceutical / Industry Driven Additional Clinical Site / Extension study		R12 198
No funding/sponsor		→ skip to Q. 5

Note: The HREC does not have the authority to waive the ethics review levy. If a waiver is required, please contact Mr Salie Nassiep, the Research Management Accountant in the Faculty of Health Sciences (021 406 6409) email: salie.nassiep@uct.ac.za

4.5 Where applicable, has the PI negotiated an agreement with the hospital or other health or laboratory services to cover the costs of interventions/ procedures/ investigations performed solely for research purposes? (e.g. extra MRIs, CT scans, diagnostic tests, prolonged hospitalisation, use of non-research staff to collect research-related data or perform research-related procedures) **(tick ✓)**		
☐√ N/A	☐ Yes	☐ No
If no, please explain how research costs will be recovered		

5. Characteristics of the protocol

5.1 Category of research Please select an appropriate category for your protocol. If the protocol falls in more than one category please designate a primary and secondary category by entering a '1' and a '2'.	
Medical intervention/ clinical trial (e.g. medicines, traditional or complementary medicines, nutriceuticals, devices or innovations)	
Behavioural/ psychosocial interventions (e.g. comparison of counselling programmes)	
Epidemiology/ observational study (e.g. survey, prevalence, case control, cohort studies)	
Quality improvement	
Testing new technologies	
Medical record review, audit	
Establishment of a specimen repository, medical data base/ registry	
Clinical laboratory studies	
Clinical laboratory studies (DNA related)	
Qualitative research (e.g. focus groups, in-depth interviewing, ethnography)	
Pilot study	√
Other. Please describe:	

5.2 BIOHAZARD STATEMENT

Important: All researchers must be aware of and familiar with the MDSS Safety Sheets for each of the compounds/organisms used in this study.

Note: Faculty Biosafety Committee approval is required for all projects involving biohazardous material that poses a real or potential risk to human health and/or the environment.

Examples include transfer of rDNA, DNA, or RNA into whole animals or plants; use of human or animal pathogens (BSL2 and higher); use of genes encoding toxins that are lethal for vertebrates; and release of GMOs into the environment.

Will this application require **approval** by the **Faculty Biosafety Committee**? If yes, please note that you are required to submit an application for approval to the Faculty Biosafety Committee / GMO committee. Please consult the Faculty Research webpage at: http://www.health.uct.ac.za/fhs/research/faculty-biosafety-committee	☐ Yes	☐ √ No

5.3 Does the study involve innovative therapy? Innovative therapy is a newly introduced or modified therapy with unproven effect or side effect, and is being delivered in the best interest of the patient. While there are clear distinctions in the aims of research and care, innovative therapy is experimental in nature and may involve data collection, similar to that for research. The HREC needs to determine whether the planned intervention can be classed as research.		☐ Yes	☐ √ No
5.4 Category of participants	☐√ Adults	☐ Minors (<18 years)	
		Please specify age range:	

5.6 Estimated number of participants to be enrolled at the local site.	Number of Adults:	40	Number of Minors:	

5.7 Estimated duration of the study.	2 weeks

5.8 Location(s) of the study: (Please supply name of the Research Unit / Site and/or Hospital/Institution and particular department – if applicable)
Groote Schuur Hospital, Ophthalmology theatre

5.9 Which authority will be approached for institutional approval? **Note**: Institutional approval/permission must be obtained before study commencement and must be obtained from the institution where the research data is being collected e.g. Hospital, School, Clinic, Department of Education, Provincial Department etc. prior to starting the project.

Heads of departments (Ophthalmology and Anaesthesia) and Dr Patel (Hospital approval) Groote Schuur Hospital

5.10 Please describe where and how recruitment will take place; and who will be recruited?
All patients presenting for elective eye surgery, where surgery has an expected duration of at least one hour, will be recruited on the anaesthetic premedication round by the anaesthetist doing the next days list.

5.11 Who will be responsible for recruiting participants in this study? **Note:** If the clinician involved in standard of care will be involved in this study and the recruitment of participants, please explain how the potential for therapeutic misconception will be minimized or avoided.
The recruiting will be done by the clinician involved in standard of care. This study is not therapeutic and involves only non invasive measurement of skin temperature.

5.12 Will non-English speaking/non-English fluent participants be enrolled in the study? (tick ✓)			
☐√ Yes	☐ No	☐ N/A	
If Yes, please **tick** ✓ what measures will be used to promote participants' and families' understanding:			
Written translation of consent/assent forms into a local language?	☐ √Afrikaans	☐ IsiXhosa	☐ Other (specify):
Use of trained translator(s)/ interpreter(s)	Yes		
Other. Please specify below and describe how the investigators intend to explain the study to potential participants and ensure their understanding:			

If the participant is not fluent in English the study will be explained in a language that the participant is fluent in, if a trained person can be found to explain the study to the participant. If adequate communication can not be achieved the patient will not be enrolled in the study.

5.16 What measures will be taken to protect individual privacy and the confidentiality of data?

Please see related SOPs for guidance: Privacy and Confidentiality and Collection and Storage of Data or Biological Specimens for Research Purposes

All data will be recorded on a single feasibility study data form according to random participant ID number.

This data will be captured on a single Excel spread sheet that will be stored in a password protected Dropbox folder. There will be no record connecting the participant ID or information to a specific person.

6. Clinical trials	Is this protocol a clinical trial (tick ✓):	☐ Yes ☐ NoV (If no, please go to Q.7)

This section must be completed **only** if the research involves a clinical trial of drugs/ medicines, herbal, complementary indigenous therapies; or a substance testing a clinical outcome, therapeutic devices; an innovative therapy or intervention; off-label use or a departure from standard treatment or care.

The SA GCP Guidelines (2006) define a clinical trial as any investigation in human participants intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s) and/or to study absorption, distribution, metabolism and excretion of an investigational product(s) with the objective of ascertaining its safety and/or efficacy.

WHO: 'a clinical trial is any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.

Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiological procedures, devices, behavioural treatments, process-of-care changes, preventive care, etc.'

6.7 Care after research

7. Statement of conflict of interest

The PI is expected to declare any existing or potential conflict of interest that may affect the scientific integrity and ethical conduct of this research. For purposes of this section, 'immediate family' means the PI's spouse or domestic partner and dependent children. **Please tick ✓ all that apply.**

7.1 No conflict of interest declared:	
I, or any member of my immediate family, **do not** have any interest related to this research (e.g. financial interest in the sponsor of the research or intervention being tested.)	√
I, or any member of my immediate family, **do not** have a proprietary interest in the product being tested in this research (e.g. patent, trademark, copyright, licensing agreement).	√
I, or any member of my immediate family, **do not** have any relationships related to this research (e.g. board membership, consultative, executive, employment) or any entity with an ownership interest in the research other than the relationship of sponsor-investigator.	√
I, or any member of my family or business partnerships, **will not** receive any payment for enrolling participants in this study.	√

7.2 Conflict of interest declared:	
As Principal Investigator of this research **I am aware of a potential conflict of interest**. Please describe and provide a plan to manage the conflict of interest in the space below:	

8. Declarations and Signatures

This application will not be processed unless all the required declarations and signatures are completed according to the Committee's Standard Operating Procedures. (see: SOP)			
8.1 Head of Department or Division My signature confirms that: i. The researcher(s)/student(s)/supervisor(s) have the skills, training (including research ethics training), experience and time to undertake this research. ii. There are adequate resources (e.g. equipment, space, support services) to perform this research.			
Signature of Head		Date	
Print name			

Note: Where the PI is also Head of Department, confirmation must be obtained from an authorised designee. PIs may not approve their own research.

8.2 Chairperson of the Departmental Research Committee (DRC) My signature confirms that: i. This research protocol has undergone peer review by a person(s) experienced in the field of study. ii. This research is well-designed and scientifically sound. iii. Where relevant, all methodological issues have been resolved to the satisfaction of the peer			
Signature of Chairperson		Date	
Print name			

Note: Where the PI is also the Chairperson of the DRC, confirmation must be obtained from an authorised designee. PIs may not approve their own research.

8.3 Principal Investigator

My signature confirms that:

i. Information in this application is true and accurate.
ii. I will begin the research only after written HREC approval is obtained.
iii. I accept full responsibility for the conduct of this research and the protection of participants' rights and welfare.
iv. I will conduct the research according to all ethical, regulatory and legal requirements stipulated in the HREC's Standard Operating Procedures.
v. I will provide progress reports to the HREC as requested, including a final closing report at the end of the research.
vi. I will notify the HREC in writing if any change to the research is proposed and await approval before proceeding with the proposed change except when urgently necessary to protect participants' safety.
vii. I will notify the HREC in writing immediately if any adverse event or unanticipated problem occurs during the research.
viii. I will allow an audit of my research if requested by the HREC.
ix. I have the time, training, experience and resources to oversee this research

Signature of Principal Investigator		Date	
Print name			

8.4 Student supervisor (if research is for a degree)

My signature confirms that:

i. The student researcher has adequate training and resources to complete the research in the allocated timeframe.
ii. The research has scholarly merit.
iii. The level of risk inherent in the study is commensurate with the student researcher's experience and the extent of oversight that I will provide.
iv. I have time, training, experience and resources to oversee this research.
v. I will meet the student on a regular basis to monitor progress and address any problems that may arise during the study.
vi. I will ensure that the research undergoes continuing review as required by the HREC, including annual progress reports, protocol amendments and a final closing report at the end of the research.
vii. If applicable, I will ensure that I report unanticipated problems or serious adverse events to the HREC.

Signature of Supervisor		Date	
Print name:			

Note: The supervisor and student researcher are jointly responsible for the ethical conduct of this research from inception to dissemination of findings.

8.5 Student (if research is for a degree)

My signature confirms that:

i. Information in this application is true and accurate.
ii. I will begin the research only after written HREC approval is obtained.
iii. I accept full responsibility for the conduct of this research and the protection of participants' rights and welfare.
iv. I will conduct the research according to all ethical, regulatory and legal requirements as stipulated in the HREC's Standard Operating Procedures.

Signature of Student		Date	
Print name	Francois Steyn		

Ethical approval for the Pilot study by the Human Research Ethics Committee

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: sumayah.arlefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

06 December 2018

HREC REF: 772/2018

Dr L Du Toit
Department of Anaesthesia
Ward D -23
NGSH

Dear Dr du Toit

PROJECT TITLE: PILOT STUDY: INCIDENCE OF INADVERTENT PERIOPERATIVE HYPOTHERMIA AND THE USE OF BODY THERMOMETRY TO PREDICT PERIOPERATIVE HYPOTHERMIA IN OPTHALMOLOGY PATIENTS (MMed-candidate-Dr F Steyn)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 December 2019.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student: Dr Francois Steyn will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

Form FHS006: Protocol Amendment

UNIVERSITY OF CAPE TOWN
IYUNIVESITHI YASEKAPA • UNIVERSITEIT VAN KAAPSTAD

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

Form FHS006: Protocol Amendment

HREC office use only (FWA00001637; IRB00001938)			
☐ Approved	☐ Type of review: Expedited	☐ Full committee	
This serves as notification that all changes and documentation described below are approved.			
Signature Chairperson of the HREC		Date	20/6/2019

Note: All major amendments must include a local **PI Synopsis** justifying the changes for the amendment. Please note that incomplete amendment submissions will not be reviewed.

Comments from the HREC to the Principal Investigator:
Thank you for your letter received 18/6/2019
Note: The approval of this protocol amendment does not grant annual approval. Please complete the FHS016 / FHS017 form for annual approval at least one month before study expiration.

Principal Investigator to complete the following:

1. Protocol Information

Date (when submitting this form)	07 June 2019		
HREC REF Number	772/2018		
Protocol title	Incidence of inadvertent perioperative hypothermia and the use of body thermometry to predict perioperative hypothermia in ophthalmology patients.		
Protocol number (if applicable)			
Principal Investigator	Leon du Toit		
Department / Office Internal Mail Address	Department of Anaesthesia and Perioperative Medicine		
1.1 Is this a major or a minor amendment? (see FHS006hlp) Major (tick box) Minor (tick box)		☐ Major	X Minor
1.2 Does this protocol receive US Federal funding?		☐ Yes	X No
1.3 If the amendment is a major amendment and receives US Federal Funding, does the amendment require full committee approval? **Note:** Any protocol amendments for **Full Committee** review MUST be submitted on the monthly HREC submission dates. (Please email an electronic copy to hrec-enquiries@uct.ac.za)		☐ Yes	☐ No

2. List of Proposed Amendments with Revised Version Numbers and Dates

Please itemise on the page below, all amendments with revised version numbers and dates, which need approval. This page will be detached, signed and returned to the PI as notification of approval. Please add extra pages if necessary.
I have attached a document with tracked changes, and a document without tracked changes where changes are indicated in by ~~strikethrough~~ and red font. I have also attached a letter with a detailed description of all changes. Changes to the protocol affect the following sections: 1. Page 1 Type of study feasibility pilot study to observational study 2. Page 2 Duration of study from 2 weeks to non specified time but rather limited to 50 patients 3. Page 3 Alteration in study data storage 4. Page 4 New study objectives 5. Pages 4-5 Planned statistical analysis. 6. Appendix 1 New CRF

3. Protocol status (tick ✓)

☐	Open to enrolment
X	No participants have been enrolled
☐	Closed to enrolment (tick ✓)
☐	Research-related activities are ongoing
☐	Research-related activities are complete, long-term follow-up only
☐	Research-related activities are complete, data analysis only

4. Proposed changes will affect: (tick ✓ all the categories that apply)

	Protocol
X	Study objectives, design (including investigator's brochure, clinical activities, study length)
☐	Study instruments, questionnaires, interview schedules
X	Sample size
☐	Recruitment methods
☐	Eligibility criteria (inclusion and exclusion criteria)
☐	Drug/device (composition, amount, schedule, route of administration, combination with other drugs/devices, safety information)
X	Data collection/ analysis
☐	Principal Investigator. (Please attach revised conflict of interest and PI declaration statements. Refer: sections 7 and 8.4 in the New Protocol Application Form FHS013)
☐	Consent form and information sheet
☐	Recruitment materials (e.g. advertisements)

☐	Administrative (e.g. change in sponsor's name, change in contact information)
☐	Other. Please specify:

4.1 In your opinion, will there be any **increase** in risk, discomfort or inconvenience to participants?	☐ Yes	X No
If yes, please provide a detailed justification/explanation:		

4.2 What follow-up action do you propose for participants who are already enrolled in the study?	
☐	Inform current participants as soon as possible
☐	Re-consent current participants with revised consent/assent forms (append)
X	No action required (no participants enrolled to date)
☐	Other. Please describe:

5. Detailed description of the change(s)

Please attach, for each amendment, a summary of all changes which clearly indicates:
Please see attached document

i. Old wording (e.g. ~~strikethrough~~ text, CHANGED FROM and CHANGED TO)
ii. New wording (e.g. *italicized*, **bold**, tracked)
iii. Detailed rationale/ justification/ explanation for each change

6. Ethics Review Levy – cost including vat

Cost for Major Amendments - R3 659.10
(Protocols funded by UCT (e.g. departmental funding / student research) and by certain grant funding organizations (e.g. MRC, NRF, CANSA,) are exempt from charges)

For invoicing purposes, please provide:

Sponsor's name	
Contact person	
Address	
Telephone number	
Email Address	

7. Signature

My signature certifies that I will maintain the anonymity and/ or confidentiality of information collected in this research. If at any time I want to share or re-use the information for purposes other than those disclosed in the original approval, I will seek further approval from the HREC.

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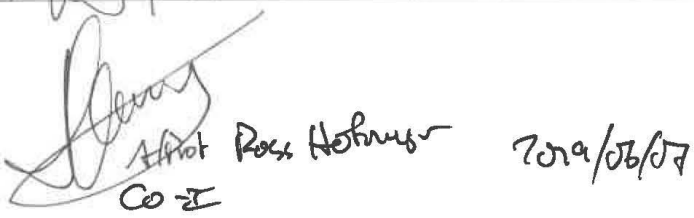
FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

Signature of PI		Date	07 June 2019



Letter to Human Research Ethics Committee stipulating amendments to original pilot study protocol for further research based on the data from the pilot study.

UNIVERSITY OF CAPE TOWN

10 Februarie 2022~~8~~
~~Februarie 2022~~

Department of Anaesthesia and Perioperative Medicine

Professorial Staff:

JLC Swanevelder MB ChB, MMed (Anes) (U Stell), FCA (SA), FRCA (Hon)
Head of Department
Email: justiaan.swanevelder@uct.ac.za
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2nd Chair of Anaesthesia
Email: bruce.biccard@uct.ac.za

Faculty of Health Science,
Anzio Road, Observatory

Human Research Ethics Committee
Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925

Dear Prof Blockman and Colleagues,

Amendment: Observational study to analyse the relationship between preoperative and intraoperative body thermometry

Attached, please find i) the fhs006 amendment form, ii) the amended protocol (one version with tracked changes and one with accepted track changes with all revisions indicated by ~~strikethrough~~ and red font).

I have detailed the description of the changes below, as requested in point 5 of fhs006.

Revision 1. Page 1.

i. Old wording:

This feasibility study aims to look at body thermometry in consecutive cases of eye surgery under general anaesthesia at Groote Schuur hospital.

ii. New wording:

This observational study aims to analyse the relationship between preoperative and intraoperative body thermometry readings in consecutive eligible cases of eye surgery under general anaesthesia at Groote Schuur hospital.

iii. Detailed rationale/ justification/ explanation:

The feasibility study (HREC 772/2018) allowed us to test the method of data collection and build the protocol for the full observational study.

Revision 2. Page 2

i. Old wording:

A planned feasibility study in the form of two-week cross-section of the proposed study population.

ii. New wording:

Prospective observational study of repeated measures of body thermometry in consecutive adult ophthalmology surgery patients at Groote Schuur Hospital.

ii. Detailed rationale/ justification/ explanation:

No longer a pilot study limited to 2 weeks but an observational study with the aim of recruiting 50 patients who fulfil the study criteria.

Revision 3. Page 3

i. Old wording:

All data will be recorded in a single feasibility study data form according to the random participant ID number. Data from the feasibility study will be captured onto a single Excel spread sheet that will be stored in a password protected Dropbox folder that only the investigators have access to. There will be no record connecting the participant ID or information to a specific person.

ii. New wording:

From the CRFs data will be captured onto a passport protected electronic database where only the study generated participant ID number can be used to link the data back to the patient. After data capturing is

completed the CRFs with attached patient consent forms will be filed together in the study folder and locked in the archive at the UCT Department of Anaesthesia and Perioperative Medicine. The folder will be kept for 5 years and labelled to be destroyed after 5 years. The cleaned electronic dataset will be uploaded to ZivaHub after publication of the study. The data will be available to other researchers on request to one of the principle investigator, at the discretion of the principle investigator. At no time will any patient identifiable information be recorded in the electronic database, used in analysis, or published in any form.

iii. Detailed rationale/ justification/ explanation:

Same confidentiality but data will be more available.

Revision 4. Page 4

i. Old wording:

The observations will be used to calculate:

1. How many participants can be studied per week? (Meet inclusion criteria.)

2. How many participants have a starting core temperature lower than or equal to 36 degrees Celsius? (Meet exclusion criteria.)

3. How many participants have a core temperature lower than or equal to 36 degrees Celsius at 1 hour? (Estimated event rate.)

4. What is the average skin temperature and body temperature before induction of anaesthesia?

5. With the amount of data we can gather during a 4-6 week study period, what would be the best statistical plan be for the primary outcome and which secondary analyses should we plan for?

ii. New wording:

Data will be summarised using mean (standard deviation), median (interquartile range), or

frequency (proportion) as appropriate for the data type.

1. Primary outcome: alternative hypothesis: Those who experience intraoperative hypothermia (core temperature <36.0°C) as measured by oesophageal thermistor have a different (lower) preoperative mean body temperature than those who do not experience preoperative hypothermia. Tested by student's t-test (or Wilcoxon rank sum test).

2. Secondary outcomes: alternative hypotheses:

a. Those who experience intraoperative hypothermia as measured by ZHF monitor have a different (lower) preoperative core temperature as measured by ZHF monitor. Tested by student's t-test (or Wilcoxon rank sum test).

b. ZHF monitoring correlates with oesophageal temperature. Tested measures linear regression and Pearson's correlation at correlated time points.

c. Preoperative thermometry correlates with intraoperative core temperatures at repeated time points. It is expected that correlation will decrease over time. Tested by Pearson's correlation at repeated time points.

d. The hazard of intraoperative hypothermia is associated with preoperative thermometry, BMI, and frailty. Tested by time to event / survival method (Cox proportional hazards or appropriate parametric model).

e. Intraoperative core temperature is associated with preoperative thermometry, BMI and frailty. Tested by repeated measures modelling (mixed effects model).

iii. Detailed rationale/ justification/ explanation:

The data from the pilot study has allowed us to formulate new primary and secondary outcomes.

Revision 5 pages 4-5

I. Old wording:

Not applicable

II. New wording:

The necessary samples size is estimated for the primary outcome. For a t-tests of difference between two independent means, using a two tailed test, an effect size d = 0.81 (based on mean 1: 35.5, mean 2: 35.8, SD: 0.37), a level of significance (α error probability) of 0.05 and power (1-β error probability of 0.8, with an allocation ratio 1:1, total sample size of 50 is required.

The study will use purposive sampling until 25 complete cases have been recorded in the smallest group. A complete case being defined as a patient with core temperature recorded until at least 60 minutes.

From the feasibility study it is anticipated that this will require 5-6 weeks of data collection time.

III. Detailed rationale/ justification/ explanation:

New sample sizing was determined from the data obtained in the previous pilot study.

Thank you for considering these amendments to the protocol.

Yours faithfully

Dr Francois Steyn

MMed candidate

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: Sumayah.arlefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

11 June 2019

HREC/REF: 772/2018

Dr L du Toit
Department of Anaesthesia & Perioperative Medicine
D23
NGSH

Dear Dr du Toit

Study Title: PILOT STUDY: INCIDENCE OF INADVERTENT PERIOPERATIVE HYPOTHERMIA AND THE USE OF BODY THERMOMETRY TO PREDICT PERIOPERATIVE HYPOTHERMIA IN OPTHALMOLOGY PATIENTS (MMed-candidate-Dr F Steyn)

Thank you for submitting the protocol amendment to the Human Research Ethics Committee dated 07 June 2019.

Before formal review, please address or respond to the following issues: -

1. Please update the Informed consent document as per the HREC SOP's.
2. Please explain all procedures, and exactly what testing is about.

Please quote the HREC REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Acceptance letter of the article by SAJAA

Francois Anton Steyn, Ross Hofmeyr, Leon Du Toit, Tristan Naidoo:

Thank you for your revised manuscript entitled "A descriptive study of the relationship between preoperative body temperature and intraoperative core temperature change in adults under general anaesthesia" which has been accepted for publication. You will be contacted by our proofreader, in due course, to finalise the editing of the manuscript.

Thank you for supporting the South African Journal Anaesthesia and Analgesia.

Yours sincerely
Prof B Biccard
Editor: SA Journal of Anaesthesia and Analgesia

toc@sajaa.co.za

Data analysis done by Tristan Naidoo, UCT Statistical Consulting Services

Francois Steyn

Initial research question:
Can we predict what the core body temperature will be after an hour of anaesthesia based on preoperative body temperatures and mean body temperatures.

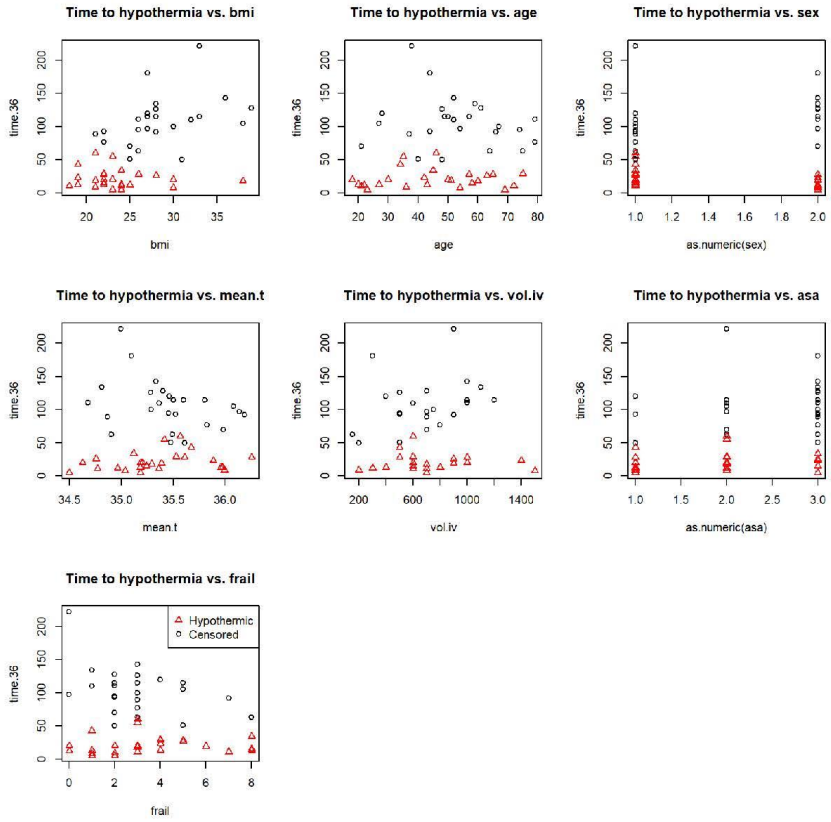
Research question in the context of survival analysis:
What is the probability of a hypothermia, after 60 minutes, given `mean.t`. Further, what other factors play an influential role in determining hypothermia after 60 minutes.

EDA:

Identifying possible explanatory variables

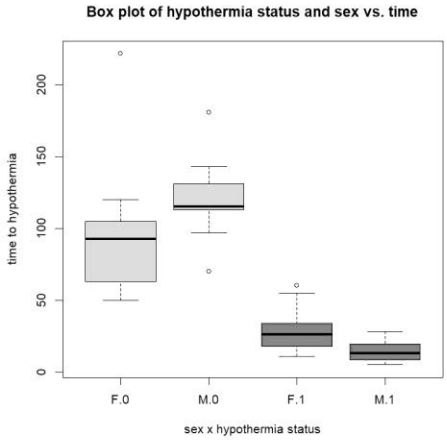
Time to event vs. independent variable plots

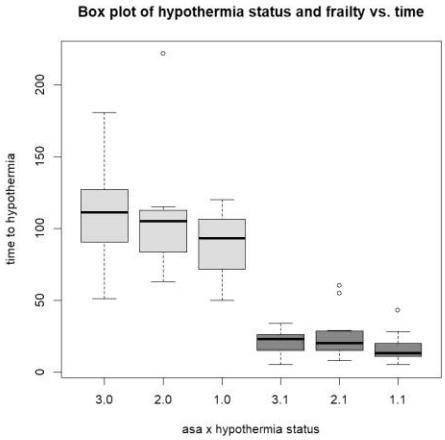
We can look across the x-axis to see if a predictor characterises hypothermia – particularly we look for an uneven spread of censored to non-censored patients. In the case of factors, we want to see if there is more censoring in one level verses another, however this is influenced by the number of subjects per factor and we will need to look at proportions if we see something interesting.

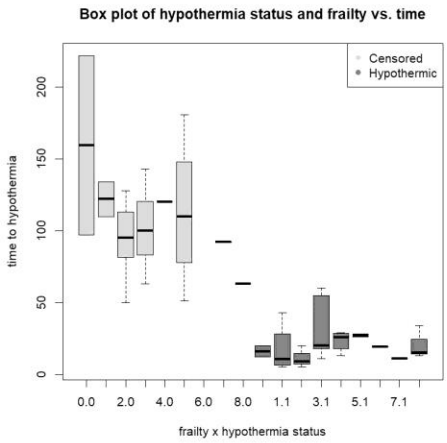


The most noticeable predictor is *bmi*. It seems plausible that lower values of *mean.t*, around 35.25, may predict hypothermia. Sex also looks interesting – this could be related to one sex having lower BMIs.

In the case of factors, box plots are more appropriate. Inspecting sex, we see below that males had shorter times to hypothermia than females and a smaller spread. Inspecting asa we see that higher scores were associated with higher mean times to hypothermia. Inspecting frailty, the experience seems to be mixed, but this may due to the apparent sparse representation of the higher levels of the factor in the dataset.



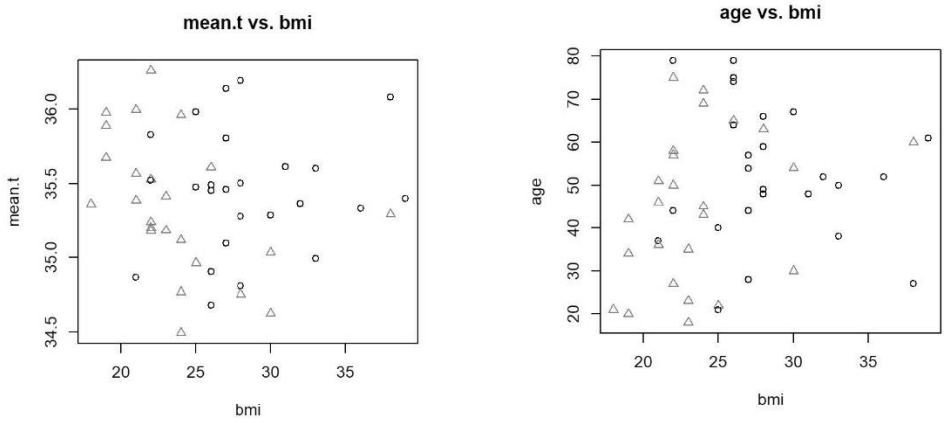




Above we considered looking at scatter plots between specific variables and the time to event; below we can look at a scatter plot of all variables vs. one another as well as the distributions of the variables. We can inspect this plot to see if there may be any interactions between the variables worth looking at.


age
bmi
sex
asa
frail
mean.t
time.36
hypo.ever
duration.anaes
vol.iv
quantile

Based on the above scatter plot above, it's looks like something may be going on with age vs. bmi and mean.t vs. bmi. Larger versions of the plots are shown below:

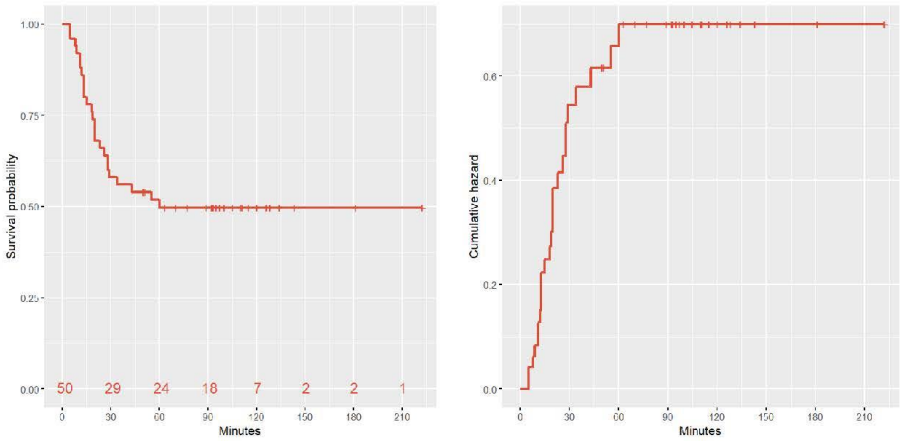


Inspecting the plots above, it appears that there may be an interaction at lower ages and bmi, however on closer inspection nothing can be seen in the mean.t vs bmi plot.

Modelling

Kaplein-Meier (KM) Statistic

To start we look at the curve created by the KM statistic – a non-parametric fit to the survival function: S(t). The survival function provides the probability that a patient would not have experienced hypothermia by time *t*. The cumulative hazard function – the integral of the hazard function – provides a measure of risk of a patient at time t.



The advantage of the KM curve is that it allows us to characterise the experience of the patients in the dataset well; however, the limitation is that it does not allow for neither the inclusion of continuous variables nor multiple independent variable. A common next step to address this is to use Cox proportional hazard (PH) model.

Cox PH Regression

$$\lambda(t|\boldsymbol{x_j}) = \lambda_0(t)\exp(\boldsymbol{x_j\beta})$$

$$\rightarrow \log(\lambda(t|\boldsymbol{x_j}) = \log(\lambda_0(t)) + \boldsymbol{x_j\beta}$$

$$e.g. \qquad = \log(\lambda_0(t)) + \beta_1 mean.t + \beta_2 bmi$$

A semi-parametric model which makes no distributional assumptions about the form of the hazard function but is a parameterised regression model.

Assumptions:

1) Proportional Hazard (PH) assumption – i.e. the effect of the predictors is time invariant
2) Linearity and additivity of covariates with respect to the log-hazard functions

(Harrell 2016)

Variable Selection:

The preceding analysis helps to find possible covariates and interactions that could be useful in explaining the response. This in addition to the domain expertise provided by the clinician is the motivation for the predictors used in models considered.

In order to choose the most appropriate model, we need to apply a variable selection technique. In the case of this analysis, a likelihood ratio statistic was use for nested models while the BIC statistic was used to compare different models.

Level 1:

At the first level we consider adding each variable separately and compare this updated model to the null model ($\lambda_0(t)\ vs.\ \lambda_0(t)\exp(\beta_1 X)$) ; this allows us to determine on which explanatory variables the model depends. The outcomes for this procedure are shown below:

LRT Results:

$$LRT: -2\log(\frac{\widehat{L_1}}{\widehat{L_2}}) \sim \chi_1^2$$

Model	Chisq	p-value	Improvement
age	3.53	0.06	Yes (@ alpha = 0.1)
asa	9.88	0.007	Yes
bmi	12.85	0.0003	Yes
frail	6.60	0.58	No
mean.t	1.29	0.26	No
room.t	1.45	0.23	No
vol.iv	0.14	0.71	No

From the above we see that the three independent variables that improved the study are: *age*, *asa* and *bmi* – looking at the previous plots of time to hypothermia vs. the independent variables this seems to be a reasonable result.

Note: frail was used as an ordinal variable – this is not ideal due to the number of levels; if we can assume that the differences between levels are the same, we can treat this variable as continuous. (Addressing comment in the code). Further, I did try coding frail as high and low but the improvement was still insignificant.

Level 2:

Based on the research question of this study, it is necessary to include *mean.t* in the model. Hence, the next level of comparisons will consider the variables found to improve the null model above, to a model including *mean.t*. In this case two LRTs are required per updated model, one to the model with mean.t only and one to the model with the added variable only:

1) $\lambda_0(t)\exp(\beta_1 \text{mean.t})\ \ vs.\ \lambda_0(t)\exp(\beta_1 \text{mean.} + \beta_2 X)$
2) $\lambda_0(t)\exp(\beta_1 \text{X})\ \ vs.\ \lambda_0(t)\exp(\beta_1 \text{mean.} + \beta_2 X)$

The results are shown below:

Model	Chisq	p-value	Improvement
mean.t vs. mean.t + age	4.07	0.04	Yes
age vs. mean.t + age	1.84	0.18	No
mean.t vs. mean.t + asa	12	0.002	Yes
asa vs. mean.t + asa	3.42	0.06	Yes (@ alpha = 0.1)
mean.t vs. mean.t + bmi	14.50	0.0001	Yes
bmi vs. mean.t + bmi	2.94	0.09	Yes (@ alpha = 0.1)

From the above we see that the three independent variables that resulted in improvement in both directions are: asa and bmi.

Level 3

The final level considers the model that consists of *mean.t, asa* and *bmi* (motivated by the result above). In this case, as before, we must make two comparisons. The results are shown below:

Model	Chisq	p-value	Improvement
mean.t + asa vs. mean.t + asa + bmi	12.10	0.0005	Yes
mean.t + bmi vs. mean.t + asa + bmi	9.61	0.008	Yes

In both comparisons we find that there is an improvement, hence the final model to be used consists of *mean.t, asa* and *bmi.*

Interactions

The next step in the model building process is to consider interactions. Based on the EDA and modelling results, the interactions considered are *asa*bmi, age * bmi* and *mean.t * bmi*. The consideration of *mean.t * bmi* is also motivated by the work done by Francois.

To compare the interactions to the current model, we can again use LRT provided the models are nested.

Considering *mean.t * bmi*:

Model	Chisq	p-value	Improvement
mean.t + bmi vs. mean.t*bmi	3.35	0.07	Yes (@ alpha = 0.1)
mean.t*bmi vs. mean.t*bmi + asa	8.07	0.018	Yes
mean.t + bmi + asa vs. mean.t*bmi + asa	1.81	0.18	No

From the above we see that the introduction of the interaction in the absence of asa results in an improvement (comparison 1). The introduction of *asa* to this model results in a noticeable improvement, however the introduction of the interaction into the model that already contains *asa* does not result in an improvement. Hence, the interaction should not be included.

Considering *asa * bmi*:

Model	Chisq	p-value	Improvement
mean.t + bmi + asa vs. mean.t + asa*bmi	1.17	0.56	No

From the above we see that introducing in interaction between *asa* and *bmi* does not improve the model.

Considering *age* bmi:*

Model	Chisq	p-value	Improvement
mean.t + bmi vs. mean.t + age*bmi	1.88	0.39	No

From the above we see that introducing in interaction between *age* and *bmi* does not result in an improvement.

Note, all these results are supported by looking at the BIC values (not reported for brevity) comparing the models with interactions to the final cox model chosen previously.

Final Model Results:

$$\lambda(t|\boldsymbol{x_j}) = \lambda_0(t)\exp(\beta_1 mean.t + \beta_2 bmi + \beta_3 asa2 + \beta_4 asa3)$$

(Baseline: asa1)

	coef	exp(coef)	se(coef)	z	Pr(>|z|)
mean.t	-1,48	0,23	0,62	-2,38	0,02
bmi	-0,18	0,83	0,06	-3,05	0,002
asa2	-0,34	0,71	0,46	0,73	0,47
asa3	-1,68	0,19	0,61	-2,76	0,01

(Baseline: asa2)

	coef	exp(coef)	se(coef)	z	Pr(>|z|)
mean.t	-1,48	0,23	0,62	-2,38	0,02
bmi	-0,18	0,83	0,06	-3,05	0,002
asa1	0,34	1,40	0,46	0,73	0,47
asa3	-1,34	0,26	0,56	-2,39	0,02

(Baseline: asa3)

	coef	exp(coef)	se(coef)	z	Pr(>|z|)
mean.t	-1,48	0,23	0,62	-2,38	0,02
bmi	-0,18	0,83	0,06	-3,05	0,002
asa1	1,68	5,34	0,61	2,76	0,01
asa2	1,34	3,81	0,56	2,39	0,02

Interpretation

An example interpretation is provided for the model with asa1 as a baseline. An increase in mean.t results in a decrease in hazard, hence lower mean.t indicates higher risk of hypothermia; bmi follows similarly to mean.t due to the negative coefficient. Looking at both asa2 and asa3 we see that if someone has either of these asa their asa status compared to asa=1, then they are less likely to experience hypothermia; however, this reduction was only significant is someone had a status of asa3. If we look at the size of the coefficients, we see that the reduction in hazard is much larger for asa3 compared asa1. This is an interesting result since, from what I understand, higher asa scores usually indicate that a subject is more unfit– perhaps this could be related to the fact that someone with higher asa could have higher bmi?

Diagnostics

Given the procedure above, the final model was found to be:

$$\lambda(t|\boldsymbol{x_j}) = \lambda_0(t)\exp(\beta_1 mean.t + \beta_2 bmi + \beta_3 asa_2 + \beta_2 asa_3)$$

The following components will be used to assess the fit of the model.

1) PH Assumption:
    a. Hypothesis test as outlined by Grambsch and Therneau (1994)
    b. Visual inspection of Schoenfeld residuals (Cleves et al. 2010)
    c. Can stratify predictors and look at individual KM curves. Can use a log-rank test on these.
2) Overall fit:
    a. Cox-Snell residuals
3) Outliers:
    a. Visual inspection of deviance residuals – helps with model accuracy
4) Influential Observations:
    a. Score residuals
    b. Dfbetas
5) Functional form
    a. Visual inspection of martingale plot

1) PH Assumption:

a) Hypothesis test:

The null hypothesis is that assumption of proportional hazards is valid. Hence, given the results below, we cannot reject the null hypothesis and we can assume that the assumption of PH holds.

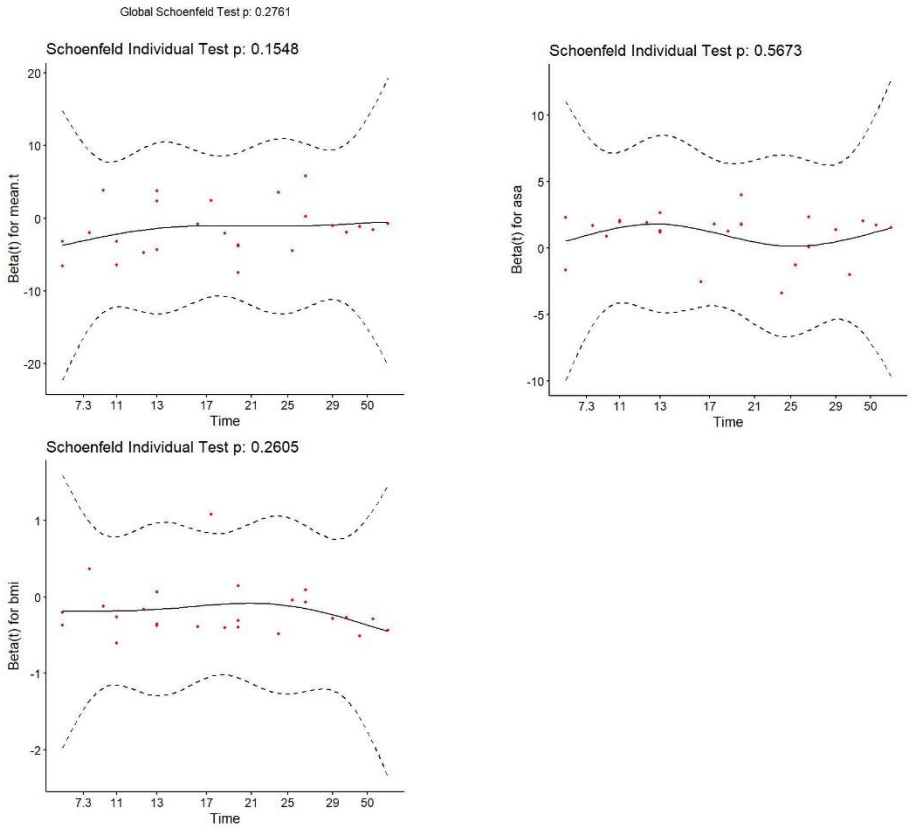
Predictor	Chi.sq	p-value
mean.t	2.02	0.15
bmi	1.27	0.26
asa	1.13	0.57
GLOBAL	5.11	0.28

b) Schoenfeld visual test:

Under the null assumption we assume that the fitted curve will have a gradient of zero, indicating that proportional hazards hold (same as above). Note the curve is a smoothing line used to help with the visual inspection.

This is usually a good test for picking up whether the ph assumption holds unless applied to a stratified proportional hazards model.

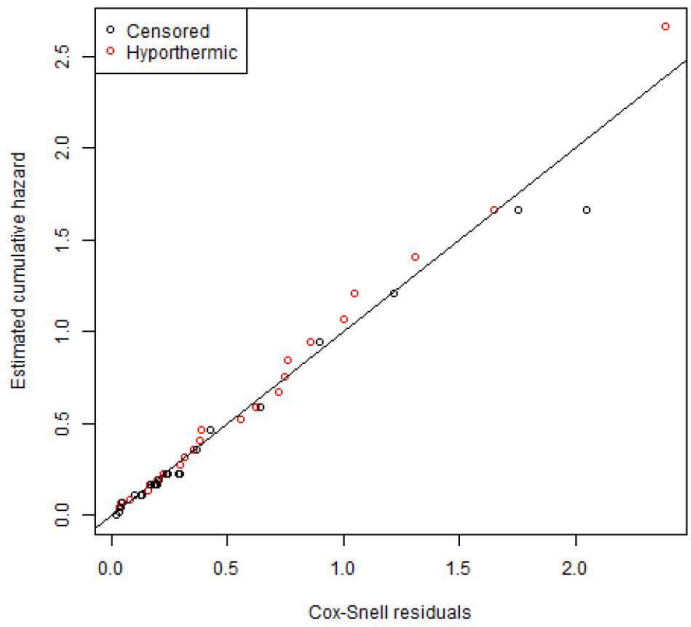
Inspecting the results, we see that we cannot reject the null hypothesis for any of the individual variables or on the global level – i.e. for the model as a whole.



Now that we have seen that the PH assumption holds, we can investigate additional diagnostics checks.

2) Cox-Snell residuals

The Cox-Snell residuals work on the fact that if the fitted model is correct, then the Cox-Snell residuals will be distributed as exp(1). In order to assess whether it's plausible that the residuals for the fitted come from an exp(1), it's possible to look at a plot of the cumulative hazard function against time; the cumulative hazard is given by $-\log(\hat{S}(r_{C_i}))$ where $\hat{S}$ is the KM estimate and r_{C_i} are the Cox-Snell residuals (Collett, 1999). This plot is shown below:

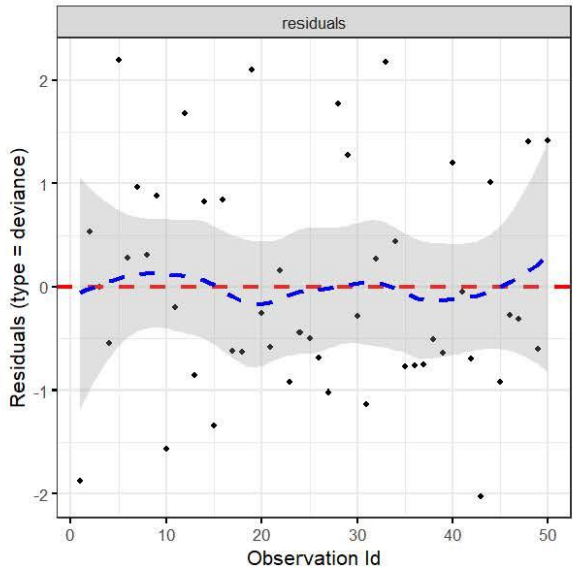


There appears to be some deviation around the line of unit slope, however this departure is not extreme. This indicates a satisfactory overall fit. A word of caution is given by Collet (1999), who states "Indeed, practical experience suggests that a fit ted model has to be seriously wrong before anything other than a straight line of unit slope is seen in the cumulative hazard plot of the Cox-Snell residuals."

3) Outliers

Deviance residual are a normalized transform of the martingale residual. These residuals should be roughly symmetrically distributed about zero with a standard deviation of 1. A positively valued deviance residual is indicative of an observation whereby the event occurred sooner than predicted; the converse is true for negatively valued residual.

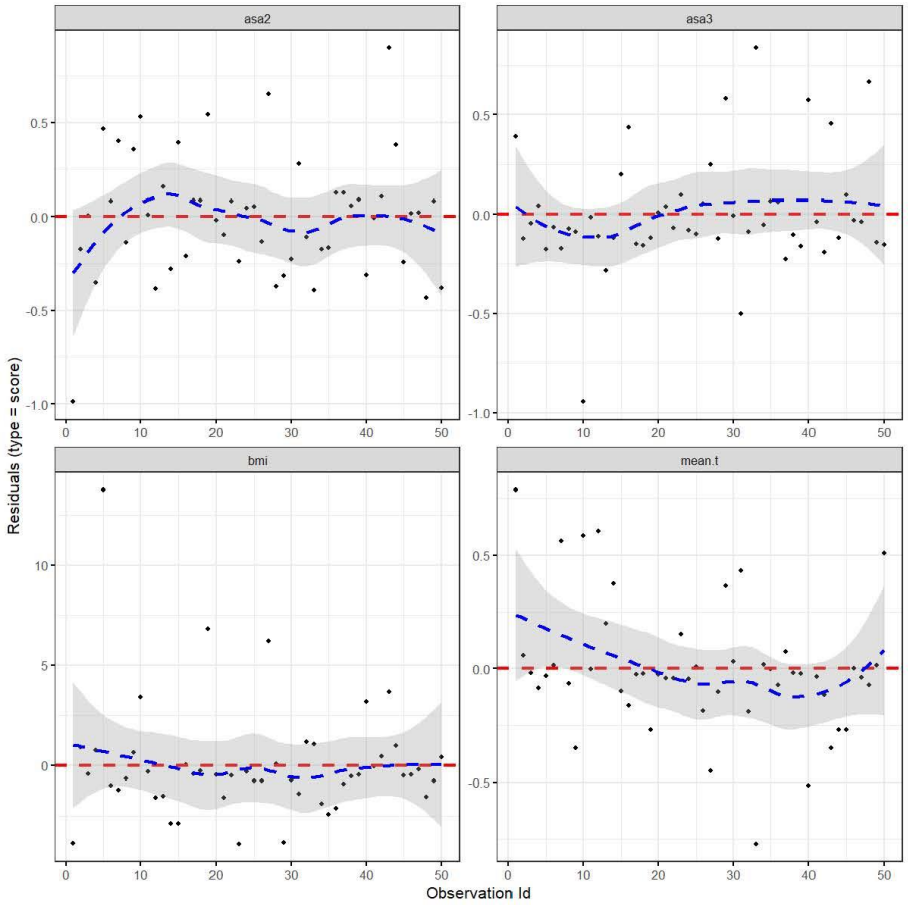
The standard deviations for the deviance residuals is 1.05 and inspecting the plot below we can visually see that the residuals are roughly symmetric around 0.



4) Influential Observations

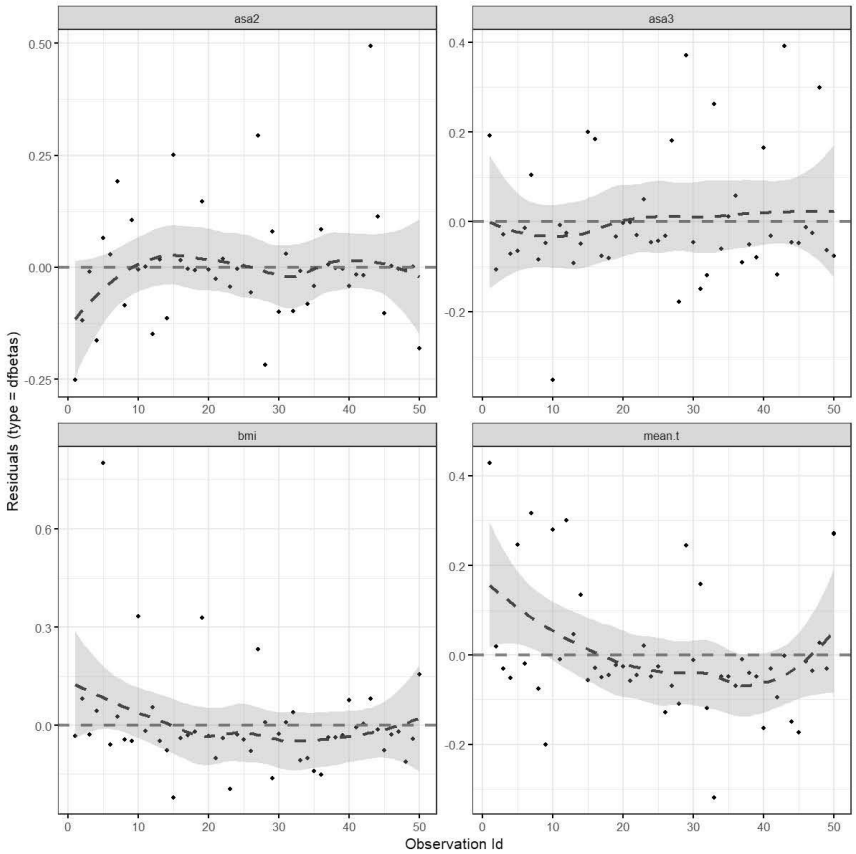
a) Score residuals:

Indicate the influence of the i^{th} observation on the betas. This plot is very similar to the dfbetas plot.



b) Dfbetas:

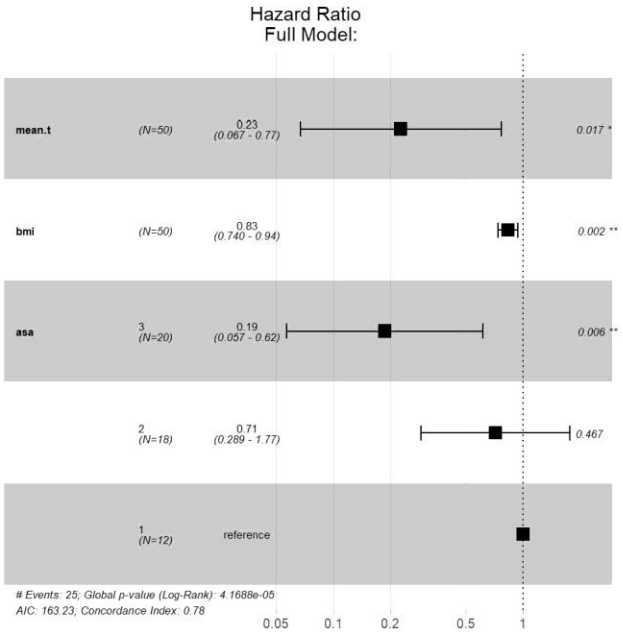
The plots report the amount the betas would change (exp(change) for change in the hazard ratio) if an observation were to be deleted. If close to 0 then the i^{th} observation has little influence of the points.

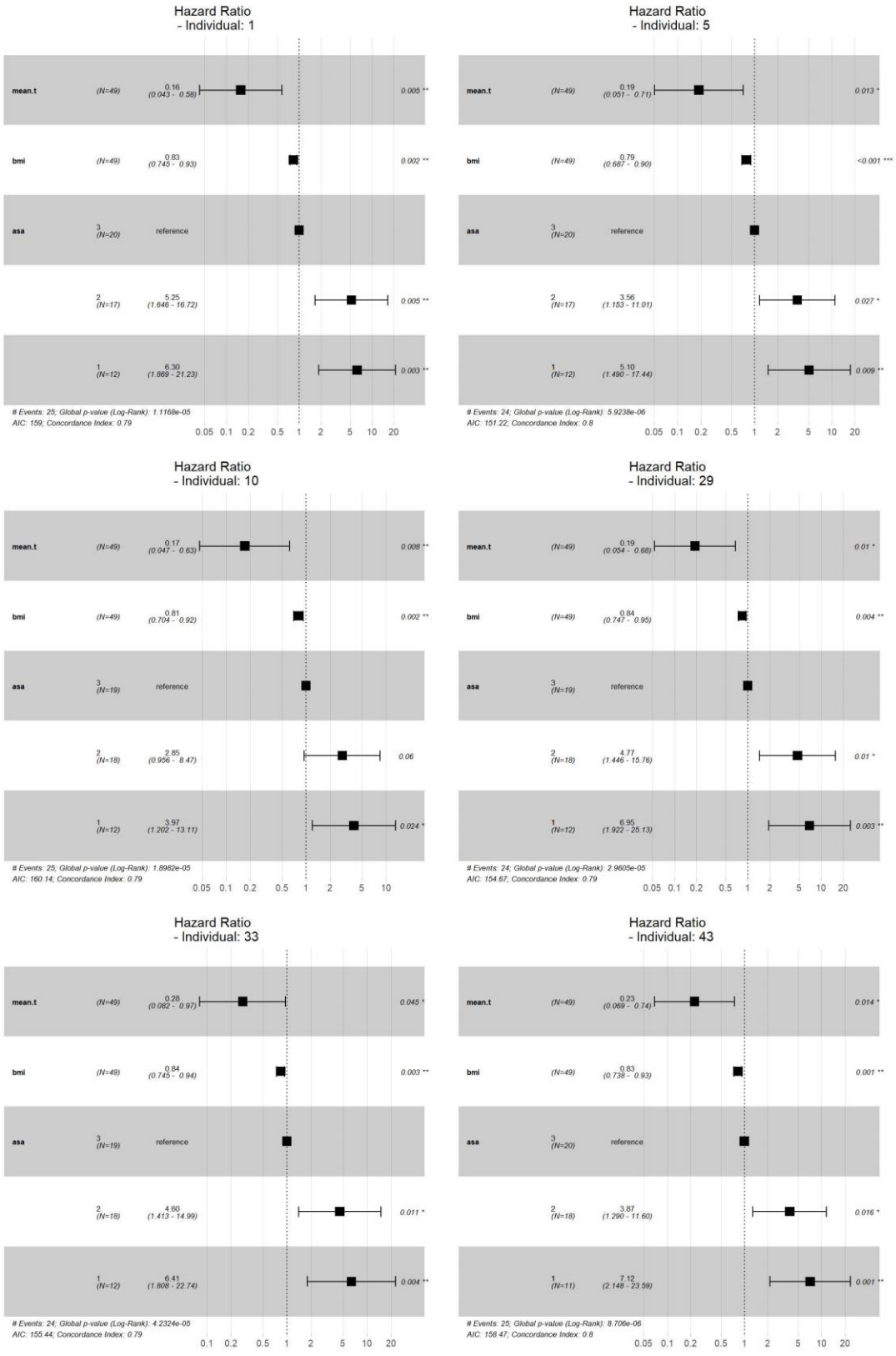


Since the dfbetas plot and the score residual plots are so similar we will only look at the dfbetas plot. If we look for the points that are influential in the extreme, we find the following:

Variable	Influencers
bmi	5
mean.t	1,33
asa2	43
asa3	10, 29, 43

The model was rerun excluding each of these points sequentially and the results are shown on the next page. The results of the full model are shown below as a reference point. The most noticeable changes occur to the asa variables when influential points are removed. (It is worth noting the image on the next page is smaller than the image below hence the bmi confidence intervals appear smaller than they are.)




Hazard Ratio
- Individual: 1
mean.t (N=49) 0.16 (0.043 - 0.58) 0.005 **
bmi (N=49) 0.83 (0.745 - 0.93) 0.002 **
asa 3 (N=20) reference
2 (N=17) 5.25 (1.646 - 16.72) 0.005 **
1 (N=12) 6.30 (1.869 - 21.23) 0.003 **
Events: 25; Global p-value (Log-Rank): 1.1168e-05
AIC: 159; Concordance Index: 0.79
0.05 0.1 0.2 0.5 1 2 5 10 20
Hazard Ratio
- Individual: 5
mean.t (N=49) 0.19 (0.051 - 0.71) 0.013 *
bmi (N=49) 0.79 (0.687 - 0.90) <0.001 ***
asa 3 (N=20) reference
2 (N=17) 3.56 (1.153 - 11.01) 0.027 *
1 (N=12) 5.10 (1.490 - 17.44) 0.009 **
Events: 24; Global p-value (Log-Rank): 5.9238e-06
AIC: 151.22; Concordance Index: 0.8
0.05 0.1 0.2 0.5 1 2 5 10 20
Hazard Ratio
- Individual: 10
mean.t (N=49) 0.17 (0.047 - 0.63) 0.008 **
bmi (N=49) 0.81 (0.704 - 0.92) 0.002 **
asa 3 (N=19) reference
2 (N=18) 2.85 (0.956 - 8.47) 0.06
1 (N=12) 3.97 (1.202 - 13.11) 0.024 *
Events: 25; Global p-value (Log-Rank): 1.8982e-05
AIC: 160.14; Concordance Index: 0.79
0.05 0.1 0.2 0.5 1 2 5 10
Hazard Ratio
- Individual: 29
mean.t (N=49) 0.19 (0.054 - 0.68) 0.01 *
bmi (N=49) 0.84 (0.747 - 0.95) 0.004 **
asa 3 (N=19) reference
2 (N=18) 4.77 (1.446 - 15.76) 0.01 *
1 (N=12) 6.95 (1.922 - 25.13) 0.003 **
Events: 24; Global p-value (Log-Rank): 2.9605e-05
AIC: 154.67; Concordance Index: 0.79
0.05 0.1 0.2 0.5 1 2 5 10 20
Hazard Ratio
- Individual: 33
mean.t (N=49) 0.28 (0.082 - 0.97) 0.045 *
bmi (N=49) 0.84 (0.745 - 0.94) 0.003 **
asa 3 (N=19) reference
2 (N=18) 4.60 (1.413 - 14.99) 0.011 *
1 (N=12) 6.41 (1.808 - 22.74) 0.004 **
Events: 24; Global p-value (Log-Rank): 4.2324e-05
AIC: 155.44; Concordance Index: 0.79
0.1 0.2 0.5 1 2 5 10 20
Hazard Ratio
- Individual: 43
mean.t (N=49) 0.23 (0.069 - 0.74) 0.014 *
bmi (N=49) 0.83 (0.738 - 0.93) 0.001 **
asa 3 (N=20) reference
2 (N=18) 3.87 (1.290 - 11.60) 0.016 *
1 (N=11) 7.12 (2.148 - 23.59) 0.001 **
Events: 25; Global p-value (Log-Rank): 8.706e-06
AIC: 158.47; Concordance Index: 0.8
0.05 0.1 0.2 0.5 1 2 5 10 20

5) Functional form

Martingale residuals are the difference between the observed number of failures in the data and the expected number of failures predicted by the model (where the expected number of failures is equal to the cumulative hazard over the period).

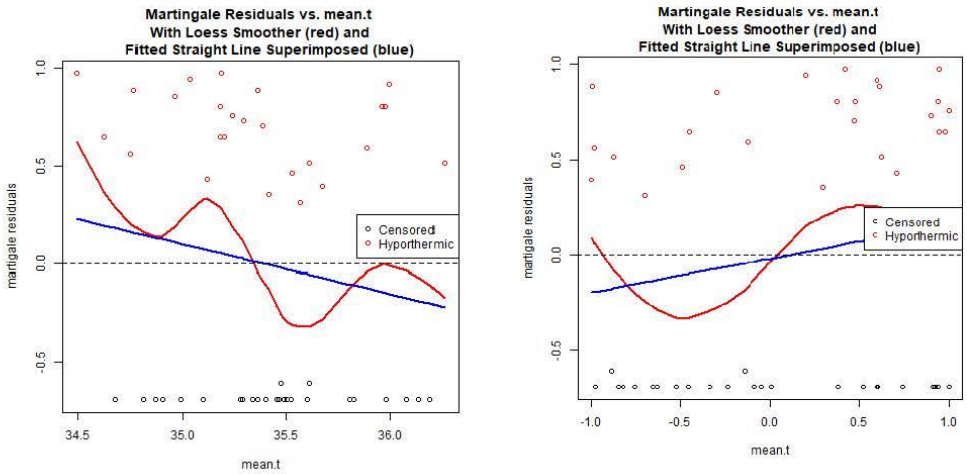
These are useful for determining the functional form of the of the predictors that enter the model. In order to address the functional form of the predictors we can plot the martingale residuals of the null model against each predictor. There is an extension to this approach, but it can only be applied when the functional form of the other predictors in the model can be assumed to be known – which is not the case in this study (Collett, 1999). This plot tests the linearity assumption of continuous predictors; a loess smoother is superimposed on the scatterplot – we expect that the superimposed line will be linear.

Note:

Martingale residuals take a value between [1,−∞] for uncensored observations and [0,−∞] for censored observations. We can use the martingale residual to test for outliers that the survival function predicts as dying to early or too late, but deviance residuals may be better for this; deviance residuals are a normalized transform of the martingale residuals.

mean.t

Inspecting the first plot below it appears that mean.t is not in the correct form. Finding an appropriate transformation was difficult due to the small range of mean.t values. The cyclical nature motivated a sin transformation – in order to increase the periodicity of the sin curve, the following transformation was used: sin(6 * mean.t). The result of the transformation is shown on the right, the transformation helped but the relationship is still non-linear. No transformation that I could find addressed the form seen below, however I did refit the model with the transformed response which appears to bet better and there was worse model performance. The loess smoother does follow the same trend as the



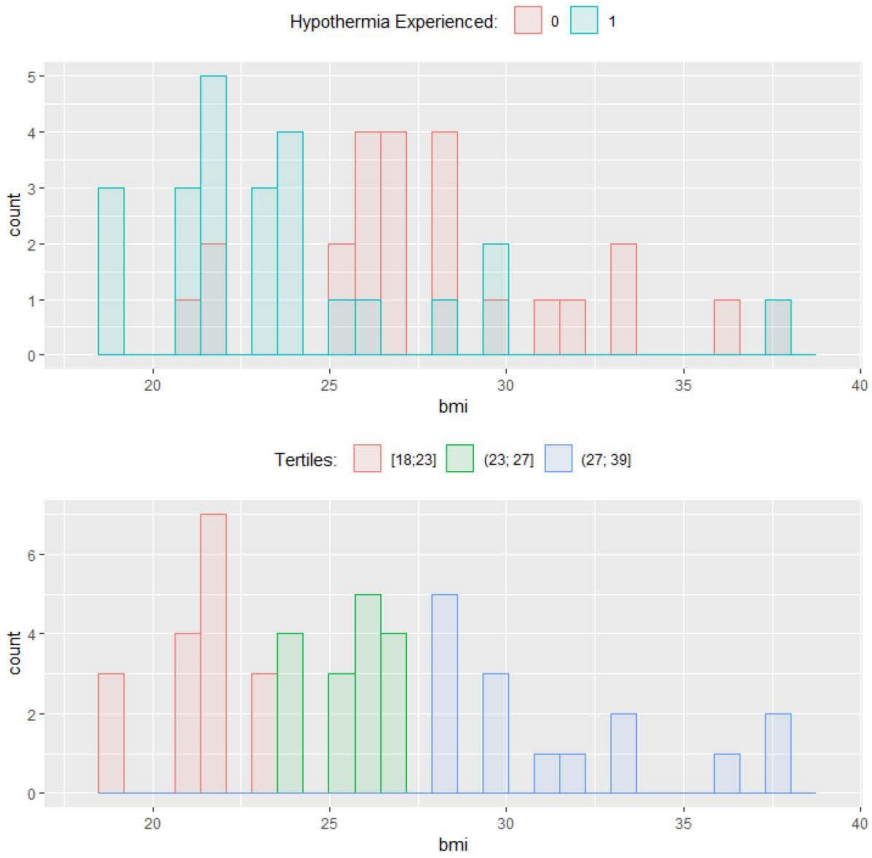
BMI Tertile Approach

Initially we use a cox proportional hazards model, with the final model chosen based on both a lowest LR and BIC criterion respectively. However, the martingale residual plot revealed interesting behaviour of bmi in the model; hence, below we investigate bmi as a categorical variable.

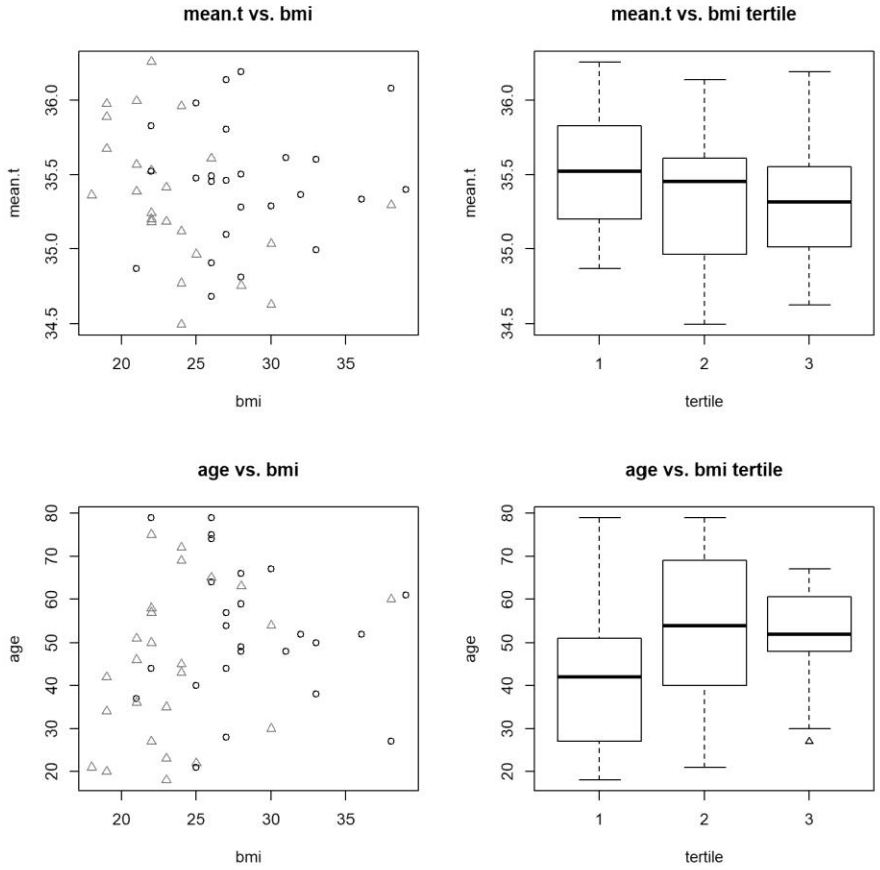
EDA

Looking at the histograms below we could argue that three profiles occur, hence motivating the choice of tertiles:

1) Mostly subjects who experienced the event
2) A mix of experience
3) Mostly those that did not experience the event



Below we again look at the interactions of bmi with age and mean.t respectively, however this time we include the bmi tertiles. Since, we're looking at tertiles, the number of subjects per factor level is the same and as such I thought it would better to look at the box plots without splitting by hypothermia status.

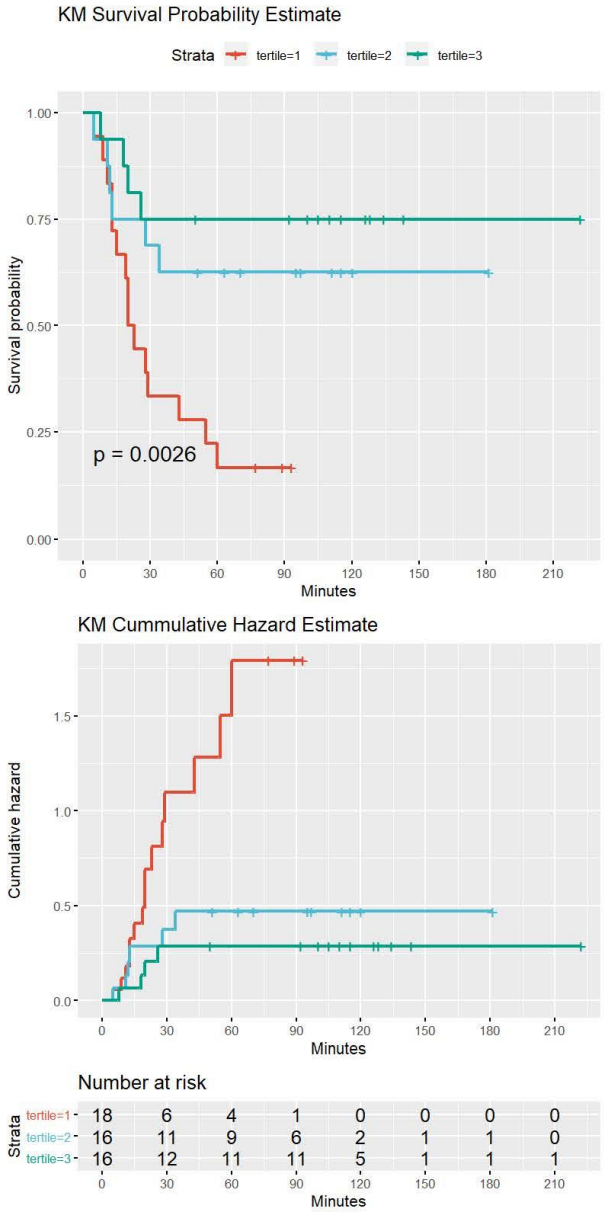


We know that the first tertile of *bmi* contains most of the hypothermia cases; inspecting the age box plot and scatter plot respectively, we see that these people on average were younger. Inspecting the mean temperature box plot and scatter plot respectively we see that the first and second tertile had similar means while the third quantile had a slightly lower mean. We also see that the first tertile had a smaller range of mean temperatures, with a higher lower bound when compared to the other tertiles.

Clearly, there seems to be different behaviour at the different tertiles of BMI, hence it's worth investigating how these tertiles influence the survival probability over time.

KM Curves:

The respective KM survival and cumulative hazard curves stratified on the bmi tertile are shown below:



(18 people in the tertile 1 due to a tie at the cutpoint)

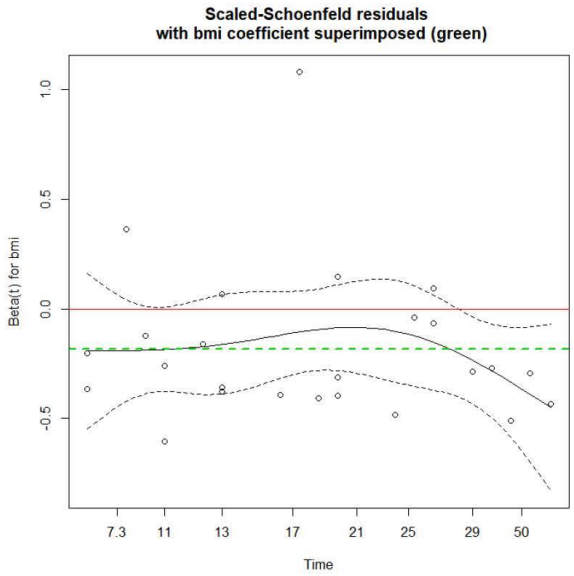
The log-rank test is significant for the *bmi* tertiles (p=0.0026 < 0.01); hence, we reject the null hypothesis that individuals with different *bmi* categories have the same survival function. This indicates that the assumption of proportional hazards for the *bmi* variable does not hold – since the survival function is directly related to the hazard function. The reason the assumption of proportional hazards previously held and but now fails, is due to the fact that it is possible for proportional hazards to hold over an entire variable despite it not holding for certain ranges of the variable. Further, the log-rank test, inspects the bmi tertiles without adjusting for other predictors which is another possible reason why we now see this result. Hence, given this result it's worth investigating if addressing this possible violation may improve the model performance.

Possible ways to deal with violation of proportional hazards assumption would be to:

1) Stratify the model based on BMI
   This would no longer assume the same baseline hazards for the different levels of the predictor. A single effect per covariate would be calculated considering each stratum. The issue with approach is that no inference can be made on the variable on which we stratify, hence it would not be applicable in this study since we're interested in understanding the effect of bmi.

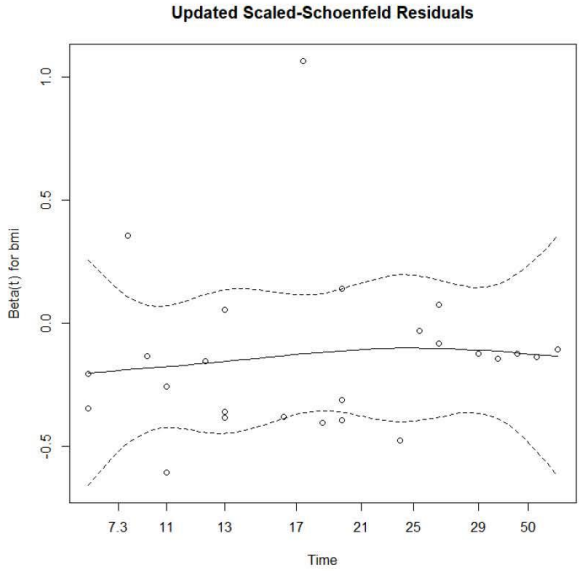
2) A time-varying coefficient
3) An AFT model

Time varying approach



Based on the plot above, perhaps we should allow β_{bmi} to change at time point 28. Note, β_{bmi} is constant after 60 minutes due to the fact that no patients reach hypothermia after 60 minutes. The BIC for this model is 168.14 – this is slightly worse that the final cox model fit earlier which had a BIC of 168.10; hence, this model does not improve on the previous cox fit.

The updated Schoenfeld residual plot is shown below, in this case we can see that the coefficients are a smoother function of time.



a) The updated hypothesis test for proportional hazards is shown below:

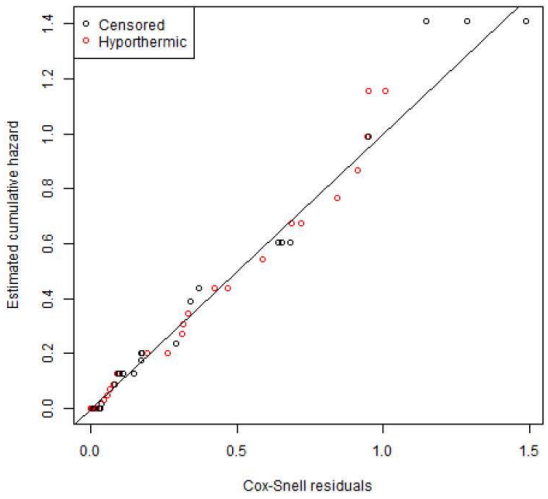
Predictor	Chi.sq	p-value
bmi	0.002	0.97
mean.t	1.23	0.27
asa	2.03	0.36
bmi:strata(tgroup)	0.85	0.36
GLOBAL	4.81	0.44

There is certainly more confidence in the ph-assumption with regards to bmi.

Model results:

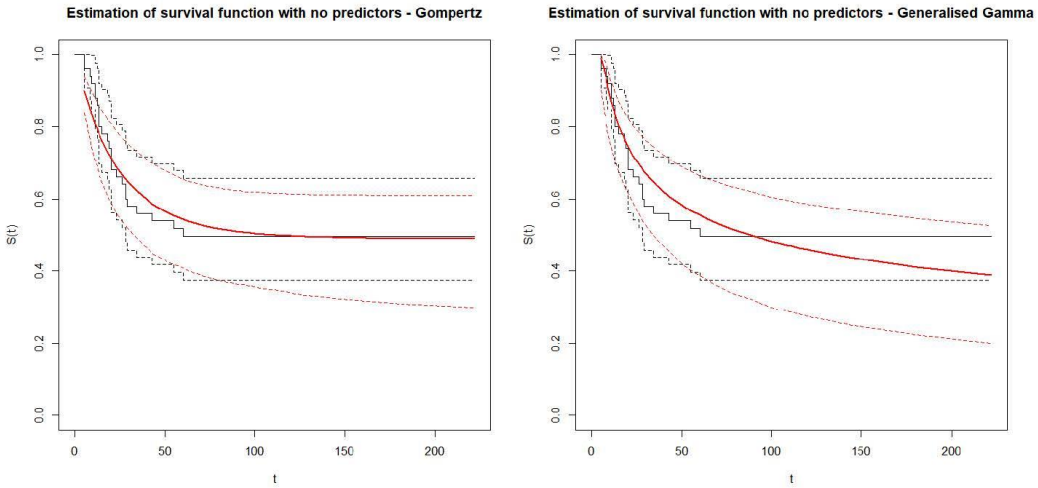
Predictor	coef	exp(coef)	se(coef)	z	Pr(>|z|)
bmi	-0,14	0,87	0,06	-2,26	0,02
mean,t	-1,43	0,24	0,62	-2,30	0,02
asa2	-0,26	0,77	0,46	-0,56	0,57
asa3	-1,59	0,20	0,61	-2,62	0,01
bmi:strata(tgroup)tgroup=2	-0,31	0,74	0,20	-1,54	0,12

Overall goodness of fit:



AFT approach

In choosing a distribution the following two distributions appeared to fit the survival function best, with the generalised gamma fitting the best according to BIC (presumably due to how well it fits the data initially compared to the Gompertz).



I tried to fit an AFT model with a generalised gamma but there was an issue inverting the Hessian and as such the parameters could not be estimated – this is possibly due to mean.t not having a strong enough influence and hence enough variation with the data. I was able to fit a model with the Gompertz distribution, but this is only available in the PH metric (Cleves et al. 2010) and hence this does not help since we're trying to address non-proportional hazards. The other distributions I tried did not achieve a reasonable fit to the data and hence given the data the data I'm not sure if it's worth the effort of trying to get the generalised gamma AFT model to fit. It's worth mentioning that I previously tried an AFT model with a Weibull distribution (despite the poor fit of the distribution) and the results were quite poor.

Summary

Initially many cox ph modes were fit. The best model had as predictors: mean.t, asa and bmi, with model selection motivated by the BIC criterion and LR test results for nested models. The initial fitting procedure and specifically the martingale residual diagnostic plot of bmi motivated further investigation of this predictor.

Bmi was split into tertiles and a log-rank test was performed on stratified KM curves, the result was that PH hazards does not hold – this was interesting since the hypothesis test based on Schoenfeld residuals did not report the same finding. In order to address this finding, a cox ph model with a time varying coefficient was fit and an AFT model was investigated. The time varying coefficient model performed similarly to the original model based on BIC; however, the Cox-Snell plot which shows overall goodness of fit appeared to be worse. In the AFT approach, it was found that the generalised gamma was the best distribution to use, however when attempting to fit this model convergence could not be achieved during the parameter optimisation procedure.

In conclusion, despite the proportional hazards not holding based on the log rank test, I would suggest still using the initial best cox ph model as the hypothesis test based on Schoenfeld residuals held. A possible reason for this discrepancy is that proportional hazards may not hold for ranges of a variable but may hold over an entire variable. The initial cox ph model based on the diagnostics and BIC value produced the best fit and had the least resistance when fitting.

I believe that the noticeably different experience of individuals with lower *bmi* as emphasised by the stratified KM survival curves show how important bmi is as a predictor and is possibly a result worth reporting on separately.

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REVIEW

A descriptive study of the relationship between preoperative body temperature and intraoperative core temperature change in adults under general anaesthesia

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Background: Despite numerous guidelines on perioperative temperature management, perioperative hypothermia remains common. Prewarming to prevent redistribution hypothermia is supported by evidence, but not widely practised. We investigate the measurement of preoperative mean body temperature as a potential tool for individualising the practice of prewarming.

Methods: We hypothesised that patients who experience intraoperative hypothermia have a lower preoperative mean body temperature. A longitudinal study was conducted in adult patients presenting for ophthalmological surgery under general anaesthesia, to describe the relationship between the incidence of hypothermia within the first hour of anaesthesia and preoperative mean body temperature.

Results: Sixty-five patients were enrolled. Twelve participants (18%) presented to the operating theatre hypothermic (core temperature < 36.0 °C). A further twenty-eight (43%) became hypothermic during the procedure. All hypothermia events occurred within sixty minutes after induction of anaesthesia, and half of the events occurred within nineteen minutes. The difference in preoperative mean body temperature between those with and without intraoperative hypothermia was only -0.2 °C (95% CI -0.4, 0.1). This is neither clinically relevant nor statistically noteworthy. In Cox proportional hazards analysis, BMI and ASA status compounded the observed association between preoperative mean body temperature and the incidence of intraoperative hypothermia. A higher BMI and ASA are associated with a lower incidence of hypothermia.

Conclusion: We conclude that intraoperative hypothermia is common and occurs early after induction of anaesthesia. We observed no useful difference in preoperative mean body temperature to help distinguish between patients who become hypothermic and those who do not. Without a useful risk prediction tool, a generic approach to prewarming remains appropriate. Preoperative screening for pre-existing hypothermia should be practised, even in cases considered as low risk.

Keywords: inadvertent perioperative hypothermia, redistribution hypothermia, mean body temperature, mean skin temperature

Introduction

Inadvertent perioperative hypothermia is defined as an unplanned core temperature of less than 36 °C occurring during the perioperative period.[1,2] It is associated with numerous adverse patient outcomes[3-5] including increased surgical site infection rates,[4-6] blood loss,[5,7] length of hospital stay[6] and cost of care.[1,8-10] Despite the ubiquity of guidelines to prevent perioperative hypothermia, the reported incidence ranges between 20 and 90%.[3,11]

In the non-anaesthetised person, peripheral thermoregulatory vasoconstriction maintains the core temperature by limiting blood flow to the skin which interfaces with the cold environment. This creates a heat exchange system with a core-to-peripheral temperature gradient, allowing the core temperature to be maintained despite mean body temperature changes.[12,13]

Mean body temperature is the average temperature of the body. Under normal thermoregulation, peripheral temperature changes to allow either heat conservation or heat loss for the purpose of maintaining a constant core temperature. With heat conservation, the gradient between the core and the skin is high and the mean body temperature is lower compared to a heat loss state, where the gradient between the core and the skin is low and the mean body temperature is higher. Anaesthesia obliterates this mechanism by causing peripheral vasodilatation and lowering the hypothalamic thresholds at which thermoregulatory vasoconstriction and shivering responses are initiated.[14] Redistribution hypothermia will occur even in the presence of intraoperative warming.[15] The heat gain from intraoperative warming is not enough to prevent the core temperature from decreasing to hypothermic levels due to the pre-existing temperature gradient between the core and the peripheries.[16] During the first thirty minutes of general anaesthesia, close to 90% of the decrease in core temperature is due to redistribution of heat from the core to the periphery. From thirty to sixty minutes, 66% of the ongoing decrease in core temperature is attributable to heat redistribution.[17] In the absence of prewarming, re-establishing normothermia after redistribution can take longer than an hour.[18] Prewarming supplies heat to the peripheries, reducing the core-to-peripheral gradient prior to anaesthesia-induced heat redistribution.[17]

Mechanistically, adverse outcomes are not only related to a single temperature measurement at the end of surgery or on arrival in the postoperative recovery area, but to the duration of hypothermia exposure.[18] Inadvertent hypothermia should be prevented at all times, making prewarming the logical gold standard.

Numerous guidelines are available on perioperative temperature management.[1,2,19,20] Prewarming is commonly recommended. Despite evidence supporting the efficacy of prewarming periods as short as 10 minutes,[21] the practice has not been widely adopted. Poor adoption has been attributed to a lack of buy-in from practitioners,[11] increase in expenses, and lack of knowledge.[11] Some day-case surgery centres claim a low incidence of hypothermia with short procedures and do not want to accrue the extra expense of an active warming device.[22]

In an age of precision medicine, guidelines should strive to be patient specific. Although some guidelines include preoperative hypothermia risk assessment, this does not translate to any specific prewarming recommendations,[1] with the exception that those found to be hypothermic preoperatively be warmed prior to induction of anaesthesia. We seek a more individualised approach to prewarming of surgical patients.

The primary objective of this study was to describe the difference in preoperative mean body temperature between patients who develop intraoperative hypothermia, and those who do not. Secondary aims included testing the effect of measured confounders on the association between preoperative body temperature and intraoperative hypothermia. Risk factors associated with inadvertent hypothermia include low ambient temperature, large surface area exposure, open body cavities, cold intravenous fluids, extremes of age, and low body mass index (BMI).[1] We hypothesised that estimated preoperative mean body temperature predicts the extent of initial core temperature decrease post induction of general anaesthesia, with patients who develop intraoperative hypothermia before sixty minutes having a lower preoperative mean body temperature than those who do not develop intraoperative hypothermia.

Methods

Study design, setting and participants

With approval of the Human Research Ethics Committee of the University of Cape Town (HREC772/2018) and the written informed consent of participants, this study was conducted at a tertiary level hospital in Cape Town, South Africa. We employed a longitudinal study design with repeated measurement of temperature over time. We used consecutive sampling of adult patients presenting for elective ophthalmic surgery requiring general anaesthesia, where the surgery had an expected duration of at least an hour. Ophthalmic surgery was selected due to minimal environmental exposure of the patients, and the lack of blood loss and fluid shifts. This was done as a method of restricting these known confounding factors from biasing the observed effect of heat redistribution after induction of general anaesthesia.

Patients were deemed eligible if they were 18 years or older. Patients with a recent fever or known sepsis were excluded. Recruitment and informed consent took place in the ward, typically on the day prior to surgery.

Variables and methods of measurement

The primary outcome was preoperative mean body temperature. Secondary outcomes were preoperative mean skin temperature and zero heat flux (ZHF) temperature. Mean skin temperature is the average temperature of the skin. Different skin regions have different temperatures which are related to blood flow and adipose distribution. In this study the mean skin temperature was calculated using the Ramanathan method.[23] ZHF temperature is a non-invasive core temperature measurement. It consists of a sensor placed on the forehead which creates a

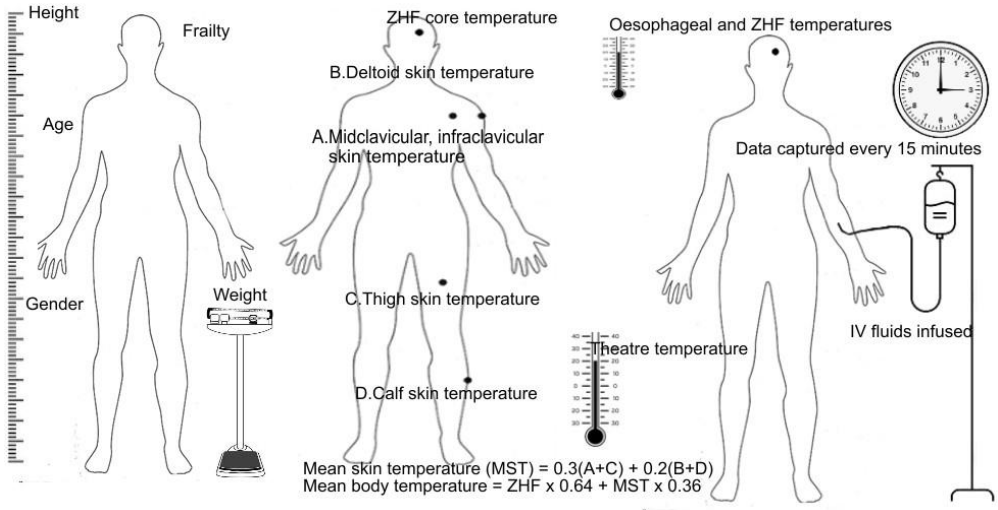

Figure 1: Measured variables. Zero heat flux (ZHF), intravenous (IV)

zone of insulation that eliminates heat loss to the environment. An isothermic pathway is formed which allows core temperature to be measured at the skin surface.[24]

Baseline variables were collected in the ward during the recruitment visit, and in the induction room of the operating theatre prior to anaesthesia. Skin temperature was measured in the induction room, using a handheld thermocouple thermometer with a surface probe (Thermapen™, Electronic Temperature Instruments Ltd., West Sussex, United Kingdom). Operating room temperature and core temperature according to a ZHF monitor (3M™ SpotOn™, St. Paul, Minnesota, USA) were recorded immediately prior to induction. Thereafter, from the time the participant was connected to monitoring in the operating theatre until the time of tracheal extubation, body core temperature was measured continuously using both the ZHF monitor and a thermistor placed in the mid-oesophagus or nasopharynx. After induction of general anaesthesia, the patient's core temperature was documented every 15 minutes. The time-to-hypothermia interval was recorded in one-minute increments. Data collection procedures during the study as well as the body sites and calculation used are described in Figure 1.

Other recorded baseline variables were patient demographics: ASA status, Edmonton frailty scale,[25] sex, age, BMI, and case-related variables: airway management (endotracheal tube or supraglottic airway), volume of intravenous fluid administered during the procedure, and duration of the procedure from induction of anaesthesia to emergence. All fluids were warmed preoperatively in a fluid warmer set at 40 °C.

Four pre-identified body sites based on the Ramanathan method,[23] were used to calculate mean skin temperature.[26] Mean body temperature was calculated using a weighted formula involving both the mean skin temperature and the core temperature (Figure 1).[23] The thermometer used for skin temperature measurements has an accuracy of 0.4 °C, within the range of -49.9 °C to 299.9 °C. During and after these measurements, the patient was covered as much as possible with a cotton blanket to prevent heat loss. The temperature sensor was applied to the skin for two minutes to allow equilibration of each reading. The ZHF sensor was attached to the forehead above the non-operative eye. The ZHF sensor has an accuracy of 0.23 °C.

The choice of anaesthetic technique and agents was left to the discretion of the attending anaesthesiologist. After endotracheal intubation, an oesophageal thermistor was placed orally at 20 cm from the teeth. The thermistor has a range of 25–45 °C and an accuracy of 0.1 °C. In cases where a supraglottic airway was used, the thermistor was placed in the nasopharynx. Intravenous fluids were limited to as little as necessary, and the volumes were recorded at the end of the case.

A forced-air warming blanket was placed over each patient but not switched on. Active warming of the patient was initiated if the core temperature dropped below 36 °C. At this point, the time to hypothermia was documented, and temperatures recorded subsequently were excluded from analysis.

Classification of hypothermia was based on oesophageal temperature, except when a supraglottic airway was used, in which case the ZHF temperature was considered a more accurate method of determination. During pilot data collection it was observed that the thermistor placed in the nasopharyngeal position in the presence of a supraglottic airway device frequently produced spurious readings. Oesophageal readings were favoured over the ZHF readings as it is a more widely used modality and its accuracy is well established. When oesophageal temperature readings were recorded below 36.0 degrees from the start of the case (baseline), the case was classified as preoperative hypothermia (left censored) and excluded from the primary analysis.

Study size

The incidence of hypothermia was unknown in this population, and no previous studies pertaining to the correlation between preoperative mean body temperature and perioperative hypothermia could be found. Therefore, a pilot study was conducted to inform our sample size calculation. The pilot study was conducted over 10 consecutive theatre days (11 February to 2 March 2019). Seventeen patients were investigated, of whom eight (57%) became hypothermic.

We used the pilot study data to estimate the required sample size for a two-sample t-test. Given an effect size of 0.3 °C difference in mean body temperature between groups (SD 0.37), to obtain power of 0.8 at a two-sided level of significance of 0.05, required a sample size of 50 patients with a ratio of 1:1. Based on this estimate it was determined *a priori* that recruitment would be continued until the smallest comparison group (with or without an incident of hypothermia) included 25 participants.

Statistical method

Baseline and outcome variables were described using summary statistics; mean (SD) for continuous variables, median (interquartile range) for ordinal variables and count (percentage) for categorical variables.

The primary objective (difference in preoperative mean body temperature between those who develop hypothermia in the first 60 minutes of anaesthesia compared to those who do not) and secondary objectives (difference in preoperative mean skin temperature and ZHF temperature between those who develop hypothermia in the first 60 minutes of anaesthesia compared to those who do not) were assessed using a two sample t-test.

A survival analysis using Kaplan-Meier estimation and Cox proportional hazards analysis was conducted to explore effects of all measured variables on the experience of hypothermia and the association between preoperative mean body temperature and hypothermia. Model building used the likelihood ratio test and Bayesian information criterion (BIC) in sequential models with increasing number of variables and first order interactions

to identify the model that best fits the data. Proportional hazards, overall fit, outliers, influential observations and functional form of variables were assessed in model diagnostics.

Statistical analysis was conducted with R (R Core Team, 2020. R Foundation for Statistical Computing, Vienna, Austria). The survival analysis made use of the 'survival'[27] and 'survminer'[28] packages. This manuscript was prepared in accordance with the STROBE statement.[29]

Results

Participants

Of the patients approached during recruitment, three did not consent and were not enrolled. A total of 65 participants were enrolled in the study during the period from 24 June until 1 August 2019.

Mean participant age and BMI were 49 years and 26.1 $kg.m^{-2}$ respectively. 54% (35/65) of the participants were female. Median ASA grade was 2. Table I reports additional details of participant and case characteristics.

Missing data: One participant's oesophageal temperature sensor produced ("non-physiological") readings; for this case data from the ZHF sensor was substituted for analysis. Data for calculating BMI was not recorded in four participants, IV fluid administered was not recorded for eight participants and the room temperature was not recorded for four participants.

Outcome data

Of the 65 enrolled participants, twelve (18.5%) were hypothermic at baseline, twenty-eight (43%) became hypothermic after induction of anaesthesia, and only twenty-five (38.5%) did not experience hypothermia. (Table II). The difference (95% confidence interval) in preoperative mean body temperature between those who developed hypothermia after induction of anaesthesia and those who did not was -0.2 °C (-0.4, 0.1) (Figure 2). The differences in ZHF temperature and mean skin temperature were -0.1 °C (-0.4, 0.1) and -0.2 (-0.7, 0.3).

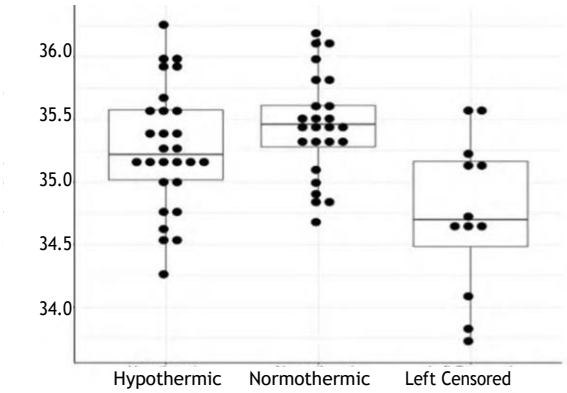

Figure 2: Box and dot plot of preoperative mean body temperature distribution by core temperature outcome during the first 60 minutes of anaesthesia. Left censored data are those participants who were hypothermic at baseline and therefore excluded from the primary outcome

Further analysis of the change in core temperature over time using a Kaplan-Meier estimate demonstrated median time (95% CI) to hypothermia as 19 (13, 23) minutes after induction of anaesthesia (Figure 3). Hypothermia events occurred early after induction of anaesthesia: 86% (24 of 28 events) occurred within 30 minutes and no events occurred after the first hour.

Table I: Participant and case characteristics reported as mean (SD) for continuous variable, median (IQR) for ordinal variables, and frequency (proportion) for dichotomous variables

	Hypothermia at baseline (n = 12)	Hypothermia during anaesthesia (n = 28)	No hypothermia observed (n = 25)
Age (years)	49.8 (14.8)	46.0 (17.1)	52.5 (15.9)
Body mass index (BMI)[θ]	26.0 (3.6)	24.0 (4.2)	28.4 (4.7)
Sex: Female	6/12 (0.50)	15/28 (0.54)	14/25 (0.56)
ASA status*	2 (2.3)	2 (1.2)	3 (2.3)
Edmonton frailty score‡	2 (1.4)	3 (2.5)	3 (2.4)
Duration of anaesthesia (min)	97 (24)	110 (45)	107 (38)
IV fluid volume (l)[Δ]	0.883 (0.252)	0.743 (0.306)	0.684 (0.279)
Room temperature (°C)[φ]	21.2 (1.1)	20.5 (1.1)	20.8 (1.3)
SGA (cp. Endotracheal tube)	1/12 (0.08)	4/28 (0.14)	2/25 (0.08)

* Maximum observed ASA status = 3. ‡ Maximum observed frailty score = 8. ASA is American Society of Anesthesiologists Physical Status Classification. IV is intravenous. SGA is Supraglotic airway device. [θ] BMI data was missing for 1 and 3 participants in the 'hypothermic before anaesthesia' and 'hypothermia during anaesthesia' groups. [Δ] IV fluid volume was not recorded for 1, 4 and 3 participants in the groups 'hypothermic before anaesthesia', 'hypothermia during anaesthesia' and 'no hypothermia'. [φ] Room temperature was not recorded for 3 and 1 participants in the 'hypothermia during anaesthesia' and 'no hypothermia' groups.

Table II: Preoperative body thermometry, mean (SD), grouped by participant experience of hypothermia during the first 60 minutes of anaesthesia

	Hypothermia at baseline (n = 12)	Hypothermia during anaesthesia (n = 28)	No hypothermia observed (n = 25)
Preoperative ZHF temperature (°C)	36.2 (0.8)	36.8 (0.5)	36.9 (0.4)
Preoperative mean skin temperature (°C)	32.8 (0.8)	32.6 (0.9)	32.8 (0.9)
Preoperative mean body temperature (°C)	34.7 (0.6)	35.3 (0.5)	35.4 (0.4)

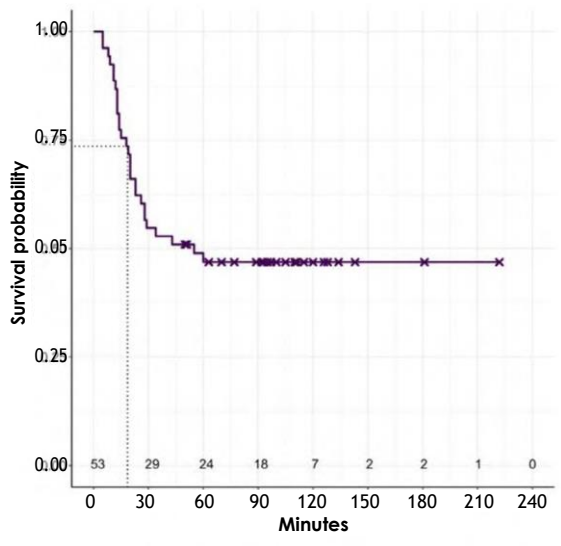

Figure 3: Kaplan-Meier plot of time to hypothermia in patients with starting core temperature greater than 36.0 °C. Median time to hypothermia is 19 minutes. Number at risk indicated at bottom of plot area along with corresponding time in minutes. Censoring events indicated with a 'x'. Survival probability on the y-axis is the cumulative probability of NOT developing intraoperative hypothermia

The results of the Cox proportional hazards analysis are summarised in Table III. Of the variables considered for inclusion in the model – preoperative mean body temperature, age, ASA, BMI, Edmonton frailty score, room temperature and volume of IV fluid infused – only preoperative mean body temperature, BMI and ASA were included in the final model as the other variables were not independently associated with the development of hypothermia or did not improve the model when comparing sequential models. Inclusion of first-order interactions did not improve the model and were not included in the final model reported here.

Table III: Final multivariable Cox proportional hazard model

	HR	95% CI	*p* – value
Preoperative mean body temperature (°C)	0.23	0.07-0.77	0.017
Body mass index (BMI)	0.83	0.74-0.94	0.002
ASA (reference: 1)			
ASA: 2	0.71	0.29-1.77	0.467
ASA: 3	0.19	0.06-0.62	0.006

The relationship between BMI and hypothermia is demonstrated in the Supplemental Figure – the hazard of hypothermia was lower in those with a higher BMI and higher in those with a lower BMI ($p = 0.002$; log-rank test).

Discussion

Key results

There was no statistically notable nor clinically relevant difference in the preoperative mean body temperature between the group who became hypothermic and the group who remained normothermic (mean [SD] 35.3 [0.5] °C and 35.4 [0.4] °C respectively). The same held true for preoperative mean skin temperature and preoperative core body temperature. Even in our relatively healthy study population of patients with nearly no body surface exposure, inadvertent perioperative hypothermia was very common (a prevalence of 62%), with an incidence of hypothermia after induction of anaesthesia of 43%.

Limitations

The study was conducted at only one institution. By design, the observed decrease in core temperature is believed to be mainly representative of redistribution hypothermia. However, the amount of heat loss to the environment was not measured. Our outcome of primary interest was preoperative mean body temperature, but there was no practical way to measure this directly in our study. Our calculation of this variable, although previously validated, could be a source of measurement error. Our data cannot be used to estimate the drop in core temperature in other types of surgery, as the amount of heat loss will be significantly higher in surgeries with more surface exposure. Although the number of enrolled participants was sufficient to address our primary objective, it remains too small to adequately explore other predictors of redistribution hypothermia. Our time-to-event analysis suggests the importance of BMI and possibly ASA status as predictors, but other measured variables cannot be excluded as determinants due to the limited sample size and restricted observed ranges of participant characteristics.

Interpretation

The high incidence of inadvertent perioperative hypothermia in our study is in keeping with findings of other researchers such as Moola *et al.*, Inal *et al.* and Sun *et al.*[3,11,18] We demonstrate this to be true even in surgery that is considered low risk, where exposure is limited, and there is minimal blood loss. The importance of preoperative screening for hypothermia has been highlighted in this study, with 19% of patients arriving at theatre hypothermic. This supports the guidance of the National Institute of Health and Care (NICE) in the UK, which states that patients should be screened preoperatively in the ward and should not be allowed to go to the operating theatre if they are hypothermic, but should instead be actively warmed until they are normothermic (except in the case of an emergency).[1]

Our study demonstrates a limitation in the understanding of redistribution hypothermia. Prewarming increases peripheral heat content and therefore decreases the core to peripheral gradient. This mechanism has repeatedly been shown to prevent redistribution hypothermia.[3,4,9,11,16,20] Our failure to demonstrate a relationship between the mean preoperative body temperature, the mean skin temperature and the core temperature to the incidence of redistribution hypothermia suggests that other important determinants exist and are commonly at play, or that these measures are not a true reflection of the core to peripheral gradient

The observed short time to development of hypothermia is noteworthy. Redistribution of heat occurs rapidly, with most of the observed events in our study occurring within 30 minutes following induction of anaesthesia. Literature typically report the incidence of hypothermia in the first hour of anaesthesia[18,30] or the absolute core temperature decrease in the first hour,[13,31] rather than time to hypothermia.

Short procedures should not be seen as low-risk for hypothermia. No hypothermic events occurred after an hour of anaesthesia, which suggests that redistribution takes less than an hour. It also suggests that the study was successful in observing only redistribution as a reason for decrease in core temperature. Other literature reports hypothermic events after an hour.[13,18,30] These studies, however, include surgeries where ongoing heat losses played a role. In these studies, the rate of temperature decrease changes at about one hour, which is further evidence that redistribution is complete at this time and that continued decrease in temperature is due to ongoing heat loss to the environment.[13,18]

Further exploration of our data using time-to-event analysis generated hypotheses about other determinants of redistribution hypothermia. Although preoperative mean body temperature was not predictive of hypothermia when assessed across the whole study sample, a lower BMI was a notable risk factor for development of hypothermia, while a higher BMI appears to have been protective. The observed data fits the hypothesis that preoperative mean body temperature becomes an important determinant of the intraoperative development of hypothermia in those with a lower BMI. This observation is in keeping with the research of Ozer *et al.* and Fernandes *et al.*[32,33]

An association with unexpected direction was observed between ASA status and the development of hypothermia, whereby those with an ASA status of 3 experienced a lower hazard of hypothermia compared to those with an ASA status of either 1 or 2. This unexpected association may be spurious, due to the relatively small dataset and restricted spectrum of participants, and interrater variability in ASA classification. The association did not appear to be solely explained by any association between BMI and ASA status. Numerous studies have looked at the relationship between ASA status and the development of perioperative hypothermia. The results are incongruent, with some studies demonstrating that ASA has an impact on the development of hypothermia[34-36] while other studies found no such correlation.[37,38] We are not aware of any studies that show a protective element with higher ASA scores. One reason for a true discrepancy may be that our design effectively studied heat redistribution, while in other studies, heat loss to the environment is the dominant determinant of body temperature.

In conclusion, inadvertent perioperative hypothermia is common, even in low-risk patients and low-risk procedures. Our findings underpin the importance of screening for preoperative hypothermia as described in the current NICE guidelines.[1] Hypothermia resulting from heat redistribution occurs early after induction of anaesthesia (within the first hour), so that prewarming (even for short procedures) should strongly be considered. Future work should explore BMI and ASA status along with other determinants of hypothermia, striving towards a patient-specific approach to perioperative warming that is informed by a better understanding of perioperative thermal physiology.

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Conflict of interest

The authors declare no conflict of interest.

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Ethical approval

With approval of the Human Research Ethics Committee of the University of Cape Town (HREC772/2018) and the written informed consent of participants, this study was conducted at a tertiary level hospital in Cape Town, South Africa.

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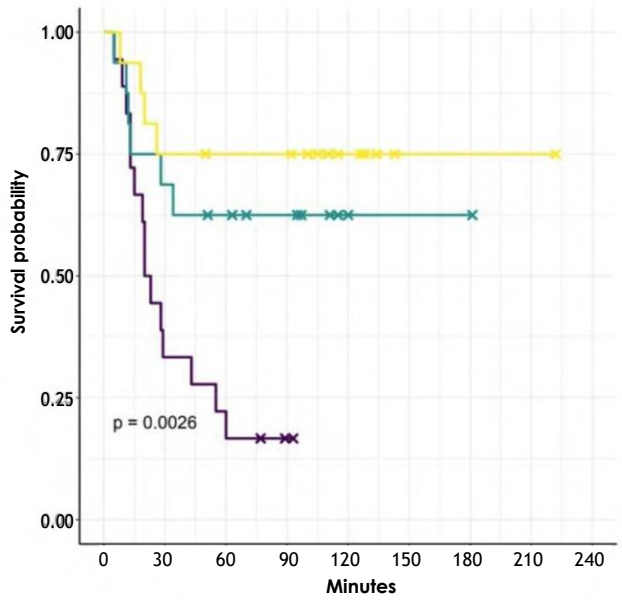
Supplemental figure:

Kaplan-Meier plot of the probability of not experiencing hypothermia stratified by tertiles of body mass index (BMI) with *p*-value for the log-rank test. Upper yellow tertile (27; 39], middle teal tertile (23; 27], lower purple tertile [18; 23]. Survival probability on the y-axis is the cumulative probability of NOT developing intraoperative hypothermia.



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