**Study Protocol**

**Study Title：**

Prediction Models for Risk Score and Prognosis of Intraoperatively Acquired Pressure Injury in Surgical Patients: a multicenter cohort study.

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**Abstract**

**Background:**

Intraoperatively acquired pressure injure (IAPI) are a prevalent and important problem in the operating room (OR), and risk recognition by a quantifiable risk score is considered urgent in patients undergoing surgical procedure.

**Objectives:**

Develop and validate a reliable and simple IAPI risk prediction model for surgical patients.

**Design:**

A prospective, multicenter, cohort study.

**Participants and setting:**

All patients who underwent surgery procedure from operating room of more than 5 tertiary hospitals in China.

**Methods:**

We will use a pre-set observational assessment scale that consists of 24 indicators to construct the predictive model in this study. In addition to these pre-set indicators, the researchers will also collect other relevant indicators that they believe may contribute to the predictive model. Primary outcome was incidence of IAPI of any stage at 7 days from operating room admission. Secondary outcomes were in-hospital mortality (follow-up endpoint is 3 months after surgical procedure), surgical complication, and hospitalization costs. The prospective cohort study dataset is divided randomly into two

subsets: a training group (80% of the data) and an internal validation group (20% of the data). The training group is used for model development, while the internal validation group remains untouched until later stages. In model development, researchers can explore different variables and test various machine learning algorithms, such as logistic regression, artificial neural network (ANN), XGBoost, support vector machine (SVM), k-nearest neighbors (k-NN), naive Bayes, gradient boosting machines (GBM), AdaBoost, Gaussian mixture model (GMM), and support vector regression (SVR). They can train and optimize these models using the training dataset. After training the models on the training dataset, researchers can evaluate their performance using appropriate evaluation metrics (e.g., accuracy, precision, recall, F1-score, area under the receiver operating characteristics curve). Based on the evaluation results, we refine the model by tweaking hyperparameters, feature selection, or employing techniques like cross-validation or grid search. This iterative process aims to find the best-performing model configuration. Once the model is optimized using the training dataset, it is then evaluated on the internal validation dataset. This evaluation serves as an unbiased assessment of the model's performance on unseen data, providing an estimate of its ability to generalize. Based on the performance on the internal validation dataset, to choose the best-performing model as the final predictive model.

**Results:**

We describe the basic clinical characteristics of the patient underwent surgical procedure, and the incidence of primary outcomes (IAPI) and attributable mortality were reported. We will evaluate the performance of the model by assessing its accuracy,

precision, recall, and other relevant metrics. We will compare the predicted outcomes with the actual outcomes to determine the model's effectiveness in correctly predicting the outcome of interest. Additionally, we may also conduct statistical analyses to identify which indicators have the strongest predictive power and contribute the most to the model's performance. The results will be presented and interpreted in the study, providing valuable information about the model's reliability and potential applicability in future scenarios. The secondary outcome of this study is in-hospital mortality, surgical complications in patients during the same hospitalization will also be reported. Additionally, we evaluated the duration of hospital stay and associated costs incurred by patients within this hospitalization period.

**Conclusion:**

A robust predictive model that can accurately predict the desired outcome.

## 1. Introduction

Pressure injury (PI, also known as pressure sores, pressure ulcers, and pressure-ulcerative wounds) is a localized injury to the skin or subcutaneous tissue, usually in areas with bony prominences, resulting from pressure or pressure combined with shear forces.[1] It is commonly found in patients who cannot change their body position to alleviate the pressure on bony projections. Intraoperative acquired pressure injury (IAPI) is a localized skin injury caused by prolonged exposure to pressure, friction, and shear forces during surgery. Most occur within 1-3 days after surgery, but they can also happen within 6 days after the procedure,[2] the incidence rate of IAPI is 4.9%~66.0%.[3,4] The most common anatomical site for developing pressure injuries is the sacrum and heels, and most cases are at stage I-II.[5-7] After PI occurs, it not only increases the physiological and psychological burden [8] on surgical patients but also affects their prognosis,[9] making it a focus of care for surgical patients.[3,4,10-12] Importantly, evidence shows that PI is associated with an increased risk of death, although PI is likely to be a result of poor health rather than the cause of death.[9,13] In particular, in critically ill patients, a single-center observational study shows that the occurrence of PI is a significant independent predictor of death,[14] and data of 1117 ICU 13254 patients from 90 countries show that patients with PI have higher mortality rates than those without PI, and the correlation between pressure injury severity and mortality rate increases gradually as the severity of pressure injury increases.[9] In addition, a retrospective study analyzing the database of inpatients nationwide in the United States found that the

mortality rate of PI patients was significantly higher than that of patients without pressure injuries.[15] Therefore, effectively identifying the risk of IAPI (infection-related complications) in surgical patients is the primary issue to address in clinical practice.

Using the PI risk assessment tool or scale is an integral part of the patient assessment process to determine if a patient has a risk of developing PI.[1] The most commonly used risk assessment tools in clinical practice at present include the Norton scale,[16,17] the Waterlow scale,[18-20] the Braden scale,[21] the Cubbin & Jackson scale,[22-24] and the Munro scale.[25] In the late 1950s and early 1960s, a team including doctors and nurses in London was committed to developing a risk assessment scale. Exton-Smith and Sherwin have shown that patients who change their body position more than 20 times per night during sleep have a lower risk of developing PI than those with less frequent changes in position.[16] Clearly, changing positions is a factor. In addition to that in 1962, several other factors such as incontinence, activity, mental state, and physical condition were added to create the first risk assessment scale (Norton scale), with a lower score indicating a higher risk of PI.[17] In the 1980s, the Norton scale played an important role in geriatric care units. A new tool, the Waterlow scale, was designed as a practical auxiliary tool for prevention and treatment while promoting understanding and identifying risk factors for patients experiencing PI, with a higher score indicating a higher risk of PI.[26] The Braden scale is a scoring system developed at the same time as the Waterlow scale, which assesses the risk of pressure injury (PI). The Braden scale is designed based on literature reviews and reports of PI etiology. Braden and Bergstrom found that key factors were pressure intensity, duration, and tolerance.[21] Other risk

factors such as changes in position, skin moisture, and nutritional status were also incorporated into the study. Each variable has three to four levels with operational definitions. Similar to the Norton scale, lower scores indicate a higher risk of PI occurrence with a "danger" threshold of ≤16 points for patients considered at high risk for developing PI. Although the Braden scale, Norton scale, and Waterlow scale all have good confidence,[27] there is conflicting study evidence on the clinical validity of these risk assessment scales, and it is unclear which of these assessments is most important for clinical practice or whether combining them will result in better patient care.[28,29] An early multicenter observational study showed that these risk assessment scales to a certain extent predicted the occurrence of PI, but the routine use of these scales would lead to inefficient use of preventive measures.[28] The latest Cochrane systematic review shows that the value of using the Waterlow scale or other scoring scales for risk assessment in terms of PI incidence or severity is very small or no value compared with clinical judgment.[29] The Cubbin & Jackson scale is a risk assessment scale developed for ICU patients, which is more suitable for the risk assessment of PI in ICU patients.[30,31] The Munro scale is a risk assessment scale specifically designed for surgical PI risk,[25] and recent studies have shown that the Munro scale has good IAPI risk assessment ability in surgical patients.[32-34] However, the Munro scale includes 15 indicators of preoperative risks, intraoperative risks, and postoperative factors. Conducting the entire scoring system will require a lot of time and effort from staff. Implementing it in a busy surgical task may be an important challenge.[35] And compared to nurses' clinical experience, this may be an inefficient work.[28]

Here, the aims of this study to develop and validate a reliable and simple surgical patient IAPI risk prediction model by a prospective multicenter cohort data based on the combination of the indicators and practical experience of the most used assessment tools.

## 2. Methods

### *2.1 Study Design*

The proposed study design is a prospective, multicenter, cohort study, which aims to calculate the risk factors that influence the incidence of IAPI. This design allows researchers to observe the natural history of IAPI, and to identify potential risk factors and interventions that may affect the incidence of IAPI.

### *2.2 Study objective*

We hypothesize that surgical patients with IAPI can be identified. The aims of this study are to develop and validate a reliable and simple surgical patient IAPI risk prediction model by a prospective multicenter cohort data based on the combination of the indicators and practical experience of the most used assessment tools.

### *2.3 Setting*

The patients will be recruited from the operating rooms of nine tertiary hospitals in China: Affiliated Hospital of Guangdong Medical University (Guangdong), First Affiliated Hospital of Sun Yat-sen University (Guangdong), Foshan First People's Hospital (Guangdong), First Affiliated Hospital of Zhengzhou University (Henan), and The First Affiliated Hospital of Nanchang University (Jiangxi).

### *2.4 Participants and Eligibility criteria*

Participants who meet the inclusion criteria: all patients who underwent surgery procedure at the participating setting after the study registration.

Exclusion criteria: Patients who have already been diagnosed with pressure injury (stage II and above) before undergoing surgery procedure. Patients/relatives/guardians understand the refusal of data to be used for clinically relevant research. Investigators believe that certain patient conditions may affect the efficacy and safety assessment of this study.

### *2.5 Variables*

#### *2.5.1 Outcome measure*

The primary outcome of this study is IAPI in patients who underwent surgery procedure. IAPI is a localized skin injury caused by the prolonged action of pressure, friction, and (or) shear forces during surgery, most occurring within 1-3 days postoperatively, and also within 6 days postoperatively.[2] The severity of pressure injuries is classified using the National Pressure Ulcer Advisory Panel Pressure Injury Staging System:[36]

- ***Stage 1 Pressure Injury: The skin is intact with erythema that does not change white in local acupressure.***

Intact skin with a localized area of nonblanchable erythema, which may appear differently in darkly pigmented skin. Presence of blanchable erythema or changes in sensation, temperature, or firmness may precede visual changes. Color changes do not include purple or maroon discoloration; these may indicate deep tissue pressure injury.

- ***Stage 2 Pressure Injury: Partial-thickness skin loss with exposed dermis.***

Partial-thickness loss of skin with exposed dermis. The wound bed is viable, pink or red, moist, and may also present as an intact or ruptured serum-filled blister. Adipose (fat) is not visible and deeper tissue is not visible. Granulation tissue, slough and eschar, are not present. These injuries commonly result from adverse microclimate and shear in the skin over the pelvis and shear in the heel.

- ***Stage 3 Pressure Injury: Full-Thickness Skin Loss***

Full-thickness skin loss, in which adipose (fat) is visible in the ulcer and granulation tissue and epibole (rolled wound edges), is often present. Slough and/or eschar may be visible. The depth of tissue damage varies by anatomical location; areas of significant adiposity can develop deep wounds. Undermining and tunneling may occur. Fascia, muscle, tendon, ligament, cartilage, or bone is not exposed. If slough or eschar obscures the extent of tissue loss, this is an unstageable pressure injury.

- ***Stage 4 Pressure Injury: Full-Thickness Skin and Tissue Loss***

Full-thickness skin and tissue loss with exposed or directly palpable fascia, muscle, tendon, ligament, cartilage, or bone in the ulcer. Slough and/or eschar may be visible. Epibole (rolled edges), undermining, and/or tunneling often occur. Depth varies by anatomical location. If slough or eschar obscures the extent of tissue loss, this is an unstageable pressure injury.

- ***Unstageable Full-Thickness Pressure Injury: Obscured Full-Thickness Skin and Tissue Loss***

Full-thickness skin and tissue loss in which the extent of tissue damage within the

ulcer cannot be confirmed because it is obscured by slough or eschar. If slough or eschar is removed, a Stage 3 or Stage 4 pressure injury will be revealed. Stable eschar (ie, dry, adherent, intact without erythema or fluctuance) on ischemic limb or heels
should not be softened or removed.

- ***Deep Tissue Pressure Injury: Persistent Nonblanchable Deep Red, Maroon or Purple Discoloration***

Intact or nonintact skin with localized area of persistent nonblanchable deep red, maroon, purple discoloration, or epidermal separation revealing a dark wound bed or blood-filled blister. Pain and temperature change often precede skin color changes. Discoloration may appear differently in darkly pigmented skin. This injury results from intense and/or prolonged pressure and shear forces at the bone-muscle interface. The wound may evolve rapidly to reveal the actual extent of tissue injury or may resolve without tissue loss. If necrotic tissue, subcutaneous tissue, granulation tissue, fascia, muscle, or other underlying structures are visible, this indicates a full-thickness pressure injury (unstageable, Stage 3, or Stage 4). Do not use DTPI to describe vascular, traumatic, neuropathic, or dermatologic conditions.

- ***Medical Device–Related Pressure Injury***

Medical device–related pressure injuries result from the use of devices designed and applied for diagnostic or therapeutic purposes. The resultant pressure injury generally conforms to the pattern or shape of the device. The injury should be staged using the staging system.

### *2.5.2 Secondary outcome*

The secondary outcome of this study is in-hospital mortality,[9] with refers to the number of patients who any cause die while receiving surgical procedure in a hospital. The data from a large sample of 13,254 patients in 1117 ICUs across 90 countries revealed that patients with pressure injuries (PI) exhibited a significantly higher mortality rate compared to those without PI. Furthermore, there was a gradual increase in the correlation between the severity of pressure injury and mortality rate.

Surgical site infections (SSIs) will also be observed, SSIs are infections of the incision or organ or space that occur after surgery.[37] Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, the subsequent statement presents the diagnostic criteria in accordance with the Third International Consensus Definition of sepsis:[38]

- Organ dysfunction can be identified as an acute change in total Sequential Organ Failure Assessment (SOFA) score ⩾2 points consequent to the infection.
- The baseline SOFA score can be assumed to be zero in patients not known to have preexisting organ dysfunction.
- ASOFA score ⩾2 reflects an overall mortality risk of approximately 10% in a general hospital population with suspected infection. Even patients presenting with modest dysfunction can deteriorate further, emphasizing the seriousness of this condition and the need for prompt and appropriate intervention, if not already being instituted.
- In lay terms, sepsis is a life-threatening condition that arises when the body's

response to an infection injures its own tissues and organs.

• Patients with suspected infection who are likely to have a prolonged ICU stay or to die in the hospital can be promptly identified at the bedside with quick SOFA, ie, alteration in mental status, systolic blood pressure ⩽ 100mmHg, or respiratory rate ⩾ 22/min.

• Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality.

• Patients with septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain mean arterial pressure (MAP) ⩾ 65mmHg and having a serum lactate level >2mmol/L (18mg/dL) despite adequate volume resuscitation. With these criteria, hospital mortality is in excess of 40%.

The surgical complications in patients during the same hospitalization will also be observed, as defined by the Clavien-Dindo classification.[39,40] Additionally, we evaluated the duration of hospital stay and associated costs incurred by patients within this hospitalization period.

### *2.5.3 Predictors*

Physiological observation indicators for all surgical patients were recorded as actual observed values within the first 24 hours preoperative, while other intraoperative observation indicators (such as anesthesia method, body temperature, blood pressure,

surgical time, blood loss, etc.) were documented based on actual observations during surgical procedures. Data collection was conducted independently using commonly employed scales for these observation indicators (Table 1):

Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable

### *2.6 Follow-up period*

The clinical follow-up will be conducted at 0.5, 2-, 24-, 48-, 72-hours and 7 days post-surgery, as well as at the three-month mark following the completion of the surgical procedure during in-hospital. The investigator has the flexibility to carry out these follow-ups either through telephone communication or in-person office visits.

## 3. Data Collection

### 3.1 Data sources and study setting

The patients will be enrolled from the operating room of nine China tertiary hospitals: Affiliated Hospital of Guangdong Medical University (Guangdong), First Affiliated Hospital of Sun Yat-sen University (Guangdong), Foshan First People's Hospital (Guangdong), First Affiliated Hospital of Zhengzhou University (Henan), The First Affiliated Hospital of Nanchang University (Jiangxi).

### 3.2 Data collection tools and instruments

The data collection will be facilitated through a network-based data infrastructure, where in the potential predictor variables are comprehensively described in Table 1. Further details can be accessed on the website https://www.wjx.cn/. Prior to sample inclusion, data collectors at all participation centers underwent mandatory homogenization training. The clinical follow-up will be conducted at 0.5, 2, 24, 48, and 72 hours post-surgical procedure, as well as at the three-month mark following the completion of the surgical procedure. The investigator has the flexibility to carry out these follow-ups either through ward visit, telephone communication or follow-up appointments for outpatient care.

**Table 1: Potential predictor variables**

| **Braden scale** |
|---|
| **1. Sensation** |
| Completely limited: unresponsive (does not moan, flinch or grasp) to painful stimuli because of diminished level of consciousness or sedation OR a limited ability to feel pain over most of body |

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| surface. |
| Very limited: responds only to painful stimuli; cannot communicate discomfort except by moaning or restlessness OR has a sensory impairment that limits the ability to feel pain or discomfort over half of the body. |
| Slightly limited: responds to verbal commands but cannot always communicate discomfort or need to be turned OR has some sensory impairment that limits ability to feel pain or discomfort in one or two extremities. |
| No impairment: responds to verbal commands; has no sensory deficit that would limit ability to feel or avoid pain or discomfort. |
| **2. Skin moisture** |
| Constantly moist: skin is kept moist almost constantly by perspiration, urine etc; dampness is detected every time patient is moved or turned |
| Moist: skin is often, but not always, moist; linen must be changed at least once a shift |
| Occasionally moist: skin is occasionally moist, requiring an extra linen change approximately once a day |
| Rarely moist: skin is usually dry; linen changed only at routine intervals. |
| **3. Activity** |
| Bedfast: confined to bed |
| Chairfast: ability to walk severely limited or nonexistent; cannot bear own weight and/or must be assisted into chair or wheelchair. |
| Walks occasionally: walks occasionally during day but for very short distances, with or without assistance; spends majority of each shift in bed or chair. |
| Walks frequently: walks outside the room at least twice a day and inside room at least once every 2h during waking hours. |
| **4. Mobility** |
| Completely immobile: does not make even slight changes in body or extremity position without assistance. |
| Very limited: makes occasional slight changes in body or extremity position but unable to make frequent or significant changes independently. |
| Slightly limited: makes frequent, though slight, changes in body or extremity position independently |
| No limitations: makes major and frequent changes in position without assistance |
| **5. Nutritional status** |
| Very poor: never eats a complete meal; rarely eats more than one-third of any food offered; eats two servings or less of protein (meat or dairy products) per day; takes fluids poorly; does not take a liquid dietary supplement OR is NPO and/or maintained on clear liquids or IV for more than 5 days. |
| Probably inadequate: rarely eats a complete meal and generally eats only about one-half of any food offered; protein intake includes only three servings of meat or dairy products per day; occasionally takes a dietary supplement OR receives less than optimum amount of liquid diet or fed by tube. |
| Adequate: eats over one-half of most meals; eats a total of four servings of protein (meat, dairy products) each day; occasionally refuses a meal but will usually take a supplement if offered OR is on a tube feeding or TPN regimen, which probably meets most of nutritional needs. |
| Excellent: eats most of every meal; never refuses a meal; usually eats a total of four or more servings of meat and dairy products; occasionally eats between meals; does not require supplementation. |

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| **6. Shear force** |
| Problem: requires moderate to maximum assistance in moving; complete lifting with- out sliding against sheets is impossible; frequently slides down in bed or chair, requiring frequent repositioning with maximum assistance; spasticity, contractures or agitation leads to almost constant friction. |
| Potential problem: moves feebly or requires minimum assistance; during a move, skin probably slides to some extent against sheets, chair, restraints or other devices; maintains relatively good position in chair or bed most of the time but occasionally slides down. |
| No apparent problem: moves in bed and chair independently and has sufficient muscle strength to lift up completely during move; maintains good position in bed or chair at all times. |
| **Waterlow scale** |
| **7. Gender** |
| Male |
| Female |
| **8. Age** |
| 14-49 |
| 50-64 |
| 65-74 |
| 75-80 |
| 81+ |
| **9. Skin type** |
| Healthy |
| Tissue paper (thin/fragile) |
| Dry (appears flaky) |
| Oedematous (puffy) |
| Clammy (moist to touch)/pyrexia |
| Discoloured (bruising/mottled) |
| Broken (established ulcer) |
| **10. Body Mass Index（BMI）Build/weight for height** |
| Average – BMI 20-24.9 |
| Above average – BMI 25-29.9 |
| Obese – BMI > 30 |
| Below average – BMI < 20 |
| **11. Nutritional Element** |
| Unplanned weight loss in past 3-6 months |
| < 5% score 0, 5-10% score 1, >10% score 2 |
| BMI >20 score 0, BMI 18.5-20 score 1, BMI < 18.5 score 2 |
| Patient/ client acutely ill or no nutritional intake > 5 days |
| **12. Tissue Malnutrition** |
| Multiple organ failure/terminal cachexia |
| Single organ failure e.g., cardiac, renal, respiratory |
| Peripheral vascular disease |
| Anaemia (Hb < 80 g/L) |
| Smoking |

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| **13. Continence** |
| Complete/catheterised |
| Incontinent urine |
| Incontinent faeces |
| Doubly incontinent (urine & faeces) |
| **14. Mobility** |
| Fully mobile |
| Restless/fidgety |
| Apathetic (sedated/depressed/reluctant to move) |
| Restricted (restricted by severe pain or disease) |
| Bedbound (unconscious/unable to change position/traction) |
| Chair bound (unable to leave chair without assistance) |
| **15. Major surgery** |
| On table > 6 hours |
| Orthopaedic/ below waist/spinal (up to 48 hours post op) |
| On table > 2 hours (up to 48 hours post op) |
| **16. Neurological deficit** |
| Motor/sensory |
| Diabetes |
| Paraplegia |
| Cardiovascular and cerebrovascular diseases/ multiple sclerosis (MS)/ cerebrovascular accident (CVA) |
| **17. Medication** |
| Long term/high dose steroid |
| Cytotoxic |
| Anti-inflammatory |
| **Norton scale** |
| **18. Physical condition** |
| Very bad |
| Poor |
| Fair |
| Good |
| **19. Mental condition** |
| Stupor |
| Confused |
| Apathetic |
| Alert |
| **20. Activity** |
| Bed |
| Chairbound |
| Walks with help |
| Ambulant |
| **21. Mobility** |

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|---|
| Mobility |
| Slightly limited |
| Very limited |
| Immobile |
| **22. Incontinent** |
| Doubly |
| Usually (urine) |
| Occasionally |
| No |
| **Cubbin & Jackson scale** |
| **23. Age** |
| <40 |
| 40-55 |
| 56-70 |
| >70 |
| **24. Weight** |
| Average weight |
| Obese |
| Cachectic |
| Any of above and oedema |
| **25. General skin condition** |
| Intact |
| Red skin |
| Grazed/excoriated/skin |
| Necrosis/exuding |
| **26. Mental condition** |
| Awake and alert |
| Agitated/restless/confused |
| Apathetic/sedated but responsive |
| Coma/unresponsive/unpurposeful movements |
| **27. Mobility** |
| Fully ambulant |
| Walks with slight help |
| Very limited/chairbound |
| Immobile/bedrest |
| **28. Haemodynamic status** |
| Stable without inotropic support |
| Stable with inotropic support |
| Unstable with inotropic support |
| Critical with inotropic support |
| **29. Respiration** |
| Spontaneous |
| Continuous positive airway pressure (CPAP)/T-piece |

| |
|---|
| Mechanical ventilation |
| Breathless at rest/on exertion |
| **30. Nutrition** |
| Full diet + fluids |
| Light diet/oral fluids/enteral |
| Parenteral feeding |
| Clear IV fluids only |
| **31. Incontinence** |
| None/anuric/catheterised |
| Urine |
| Faeces |
| Urine + faeces |
| **32. Hygiene** |
| Competent in maintaining own hygiene |
| Maintaining own hygiene with slight help |
| Requires much assistance |
| Fully dependent |
| **Munro scale** |
| ***Preoperative Risk Factor Score*** |
| **33. Nutritional state** (Length of NPO status) |
| 12 hours or < |
| >12 hours but<24 hours |
| >24 hours |
| **34. Body Mass Index or weight** |
| <30 kg/m² (normal) |
| 30 kg/m²-35 kg/m² (underweight/obese) |
| >35kg/m² (morbidly obese) |
| **35. Weight Loss** (Weight loss in 30–180 days) |
| Up to 7.4% weight loss, no change or unknown |
| Between 7.5% and 9.9% weight loss |
| ≥10% weight loss |
| **36. Age** |
| 39 or < |
| 40-59 |
| 60 or > |
| **37. Mobility** |
| Not limited, or slightly limited, moves independently |
| Very limited, requires transfer assistance |
| Completely immobile, requires full assistance |
| **38. Comorbidity** (Identify and add 1 point for each condition) |
| Smoking/Asthma/Hypertension/Diabetes/Vascular disease/respiratory disease |
| ***Intraoperative Risk Factor Score*** |
| **39. Physical status/American Society of Anesthesiologists pre-anesthesia evaluation score** |

| |
|---|
| Healthy and mild systemic disease, no functional limitations |
| Moderate to severe systemic disease, some function limitation |
| Moderate to severe systemic disease, constant threat to life and functionally incapacitating or ASA >3 |
| **40. Anesthesia** |
| Minimum alveolar concentration (MAC), local |
| Regional |
| General |
| **41. Body temperature** (98.6°F=37°C) |
| 36.1°-37.8° (body temperature maintained) |
| >37.8° or <36.1° (+ or -2°) (fluctuated + or ->2°) |
| >37.8° or <36.1° (+ or - >2°) (maintained + or ->2°) |
| **42. Hypotension** |
| Absent or <10% change in blood pressure |
| Fluctuating or 11%–20% change in blood pressure |
| Persistent or 21%–50% change in blood pressure |
| **43. Moisture** (Skin under patient) |
| Remains dry |
| Some moisture |
| Pooled or heavy fluid |
| **44. Support surface** (Positioning aids, warming blanket, position change) |
| None/use of blanket over/stationary |
| Use of aids/blanket under/stationary |
| Shearing force/added pressure/variable position |
| **45. Position** (for surgical procedure) |
| Lithotomy |
| Lateral |
| Supine/Prone |
| ***Postoperative Risk Factor Score*** |
| **46. Length of surgery** (Total time from arrival to preoperative and departure from postoperative units) |
| Up to 2 hours |
| >2 hours & <4 hours |
| >4 hours |
| **47. Blood loss** |
| Up to 200 cc |
| 201–400 cc |
| > 400 cc |
| **Relevance of clinical nursing judgement as a contributing factor** |
| **48. Nurses are trained in surgical positions.** |
| **49. The nurse assumes the role of leading the surgical position.** |
| **50. The nurse executed the surgical positioning in accordance with the predetermined plan.** |

| **51. Other variables (at the discretion of the nurse/doctor)** |
|---|

### 3.3 Schedule of Events

The events schedule comprised three sequential stages: recruitment and screening, baseline assessment, and outcome follow-up. The primary endpoint of this study is to evaluate the clinical outcomes three months post-surgery, its follow-ups should be office visits, but telephone contact will be allowed. Data collected during all follow-up visits will include IAPI, SSI, surgical complication, death. Original source documents must be submitted for any clinical events (death, IAPI, SSI, surgical complication, within 3 months).

**Table 2 Schedule of Events in the observational cohort for this study.**

| | Recruitment & screening | Baseline assessments | Follow up | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | 0.5 hours | 2 hours | 24 hours | 48 hours | 72 hours | 7 days | 3 months |
| Informed consent[1] | X | X | | | | | | | |
| Inclusion/exclusion criteria | X | X | | | | | | | |
| Demography/ Surgical procedures | X | X | | | | | | | |
| Potential predictor variables | | X | | | | | | | |
| IAPI | | | X | X | X | X | X | X | X |
| SSI | | | | | | X | X | X | X |
| Surgical complication[2] | | | X | X | X | X | X | X | X |
| Death | | | X | X | X | X | X | X | X |

Abbreviation: IAPI: intraoperatively acquired pressure injure, SSI: surgical site infections.

[1] The informed consent should be signed prior to the surgical procedures, but is can be signed after the surgical procedures in the urgent situation.

[2] The surgical complications in patients during the same hospitalization will also be observed, as defined by the Clavien-Dindo classification.

### 3.4 Recruitment of subjects

One day prior to the surgical procedure, the perioperative nurse/investigator informed the prospective surgical participant about their potential enrollment in the observational cohort for this study. In exceptional circumstances, assessment of the patient before admission into the operating room on the day of surgery procedure remains permissible. Prior informed consent was duly obtained from either the patients themselves or their legal guardians.

### 3.5 Data collection

The clinical data of each surgical patient were collected by itinerant nurses who actively participated in the surgical procedure, and the data they collected were promptly submitted post-operation. Endpoint follow-up was conducted by dedicated personnel through telephone interviews, web-based data completion, or other appropriate methods.

### 3.6 Data management and storage

The study incorporates three pre-determined key components. The network-based data will be programmed to monitoring: adherence to inclusion and exclusion criteria, homogeneous training of evaluators, and timely completion of all required data collection (without any missed visits, studies or specimens).

The itinerant nurses will determine the form content by identifying the minimal set of measurements for specified variables, selecting documentably valid and reliable

measurements (if more than one candidate), and developing, testing, and assessing reliability of new measures as required. Experienced data coordinating center (setting in participating institutions of principal investigator) staff will then order and format items to ensure clarity, smooth flow, and minimize missing information using clear skip patterns, consistent coding for all close-ended items, and standard footers to identify form name, version date, and page number. Standard modular data forms will be identified and developed for use in both the trial and registry as needed.

The Case Report Forms (CRF) will be developed as an online electronic form, enabling investigators from individual sites to access and input data via the internet.

The data coordinating center will assume responsibility for providing training to the investigator and clinical site personnel as required. Designated monitors will receive appropriate training to effectively monitor study progress, encompassing various aspects such as adherence to protocol and accurate completion of electronic Case Report Forms (eCRFs). To ensure consistent implementation of the standard protocol, data collection, and management across sites, the data coordinating center will facilitate comprehensive on-site or web conference-based training sessions over a period of one week. These sessions aim to cover essential components of clinical staff training including: (1) Familiarization with Registry Protocols; (2) Proficiency in database systems and eCRF for local web-based data entry; (3) Competence in medical record abstraction; (4) Skillful specimen/media collection and handling; (5) Effective data handling techniques; (6) Interview techniques refinement; and finally, (7) Clear understanding of quality control expectations.

The data coordinating center will ensure that all study data is protected and maintained securely during the observation period. All observation data, including investigational data and medical records, will be stored in a secure location accessible only by authorized personnel.

The study monitor will conduct periodic site visits to review the progress of the study, verify data quality, and ensure compliance with the protocol and applicable regulations. The study monitor will also conduct consecutively enrolled data audits to ensure the accuracy and completeness of the data.

During the site visits, the study monitor will review the Investigator's study files, including subject consent forms, screening records, and observation-related correspondence. The study monitor will also examine the medical records of study subjects to confirm their eligibility, the conduct of procedures, and the treatment provided.

The study monitor will communicate any observations or concerns to the Investigator/site and data coordinating center in a timely manner. The Investigator/site will have the opportunity to respond to these observations or concerns and provide explanations or clarifications.

In the event of non-compliance with the protocol or applicable regulations, the trial monitor will work with the Investigator/site and data coordinating center to develop and implement corrective actions to address the issue. The trial monitor will continue to monitor the trial until the issue is resolved and will report back to the data coordinating center on the status of the corrective actions taken.

The study monitor's responsibilities do not end with the completion of the trial. After the study is complete, the trial monitor will assist in closing out the trial, including data verification, final report preparation, and auditing of study records.

## 4. Data Analysis

### *4.1 Sample size*

The primary outcome of this study is IAPI in patients who underwent surgery procedure. The fixed position of surgical patients in the surgical procedure, and the occurrence of IAPI risk is time-dependent,[41] which it is positively correlated with the advancement of time and the occurrence of IAPI events in surgical patients.[42] For time-to-event outcomes,[43] ensure the sample size is enough to: Estimate the overall outcome proportion with sufficient precision at one or more key time-points in follow-up; Target a shrinkage factor of 0.9; Target small optimism of 0.05 in the apparent $R^2$ Nagelkerke. The formula provided by Riley et al. is as follows:

Time-event-outcome, the sample size (number of participants, n) required to achieve the expected uniform contraction coefficient S can be expressed as:

$$n = \frac{P}{(\mathrm{S}-1)\mathrm{In}\left(1-\frac{R_{cs}^2}{S}\right)}$$

To calculate the sample size, to ensure that the expected optimistic value of $R^2$ (i.e., $\mathrm{R}_{cs}^2/\max(\mathrm{R}_{cs}^2)$) has a smaller expected optimism. For time-event-outcome, the first step is to calculate the contraction coefficient corresponding to the expected optimistic value in $R^2$Nagelkerke:

$$S = \frac{\mathrm{R}_{cs}^2}{\mathrm{R}_{cs}^2 + \delta\max(\mathrm{R}_{cs}^2)}$$

The recent randomized controlled trial results showed an incidence of IAPI (stage I and above) of 13.9%,[44] assuming 0.05 acceptable difference in apparent & adjusted

R-squared. The study used the R4.1.2 software (pmsampsize package) to estimate the minimum sample size required to develop the new model. Minimum sample size required for new model development is 4115, with 572 events (assuming an outcome prevalence = 0.139) and an Events per Predictor Parameter (EPP) is 23.83. In addition, according to the pre-model design requirements, the total sample was divided into 80% samples for the development of the new model and 20% samples for the validation of the model. This means that a total of 5144 cases are required. Considering a possible 10% loss of follow-up, the minimum sample size required for the prediction model was 5658 cases.

```
NB: Assuming 0.05 acceptable difference in apparent & adjusted R-squared
NB: Assuming 0.05 margin of error in estimation of intercept
NB: Events per Predictor Parameter (EPP) assumes prevalence = 0.139

           Samp_size Shrinkage Parameter CS_Rsq Max_Rsq Nag_Rsq
Criteria 1      4115     0.900        24  0.051   0.553   0.092
Criteria 2       833     0.648        24  0.051   0.553   0.092
Criteria 3       184     0.900        24  0.051   0.553   0.092
Final           4115     0.900        24  0.051   0.553   0.092
             EPP
Criteria 1 23.83
Criteria 2  4.82
Criteria 3  1.07
Final      23.83

 Minimum sample size required for new model development based on user inputs = 4115,
 with 572 events (assuming an outcome prevalence = 0.139) and an EPP = 23.83
```

### *4.2 Data analysis*

This study is divided into two distinct sections. The aim of the first part is to create and validate a IAPI risk score for individuals from the whole cohort, predicting their individual IAPI values using a combination of potential predictive variables. The aim of the second part is to evaluate whether the IAPI score is helpful in predicting 90-day mortality in individuals from the whole cohort. We also evaluated the incidence and attributable mortality to IAPI, SSI, and surgical complications in patients admitted for

surgical procedures during the same study period.

All statistical analyses were performed with R (the latest version; R Foundation for Statistical Computing) and Python (the latest version; Python Software Foundation). All tests conducted in this study were 2-tailed, and $P<0.05$ was deemed statistically significant.

### *4.2.1 Model development*

The entire cohort is randomly divided into two datasets: a training cohort (80%), which will potentially be utilized for training twelve machine learning models and optimizing their parameters, and an internal validation cohort (20%), which was employed to evaluate the developed models on unseen data and refine the hyperparameters.

The variable selection process in the development sample will be conducted using a recursive feature elimination (RFE) algorithm.[45] RFE ranks the most relevant predictors in a dataset by training models with and without all potential predictor combinations. To identify the optimal number of variables, we will assess the incremental gain in predictive performance associated with each variable and stop at the inflexion point. RFE is an iterative process that starts with all possible features in the dataset and progressively removes the least relevant features, building a model after each iteration. The goal is to find the optimal subset of features that maximizes the predictive power of the model. In each iteration, RFE evaluates the performance of the model with and without a specific feature and removes the feature if its removal results in a significant improvement in model performance. This process is repeated until the

desired number of features is reached or a stopping criterion is met. The inflexion point is the point at which the incremental gain in predictive performance begins to decrease significantly. Identifying the inflexion point helps to ensure that the final model does not overfit the data and can generalize well to new data.[46] In conclusion, by using the RFE algorithm and identifying the inflexion point, the development sample will undergo a thorough variable selection process, ensuring that the final model is as predictive as possible while avoiding overfitting.

After variable selection with RFE, we will be trained potential seven statistical models with centred and scaled selected predictors because of the different scales of the predictors and to ease the intercept of models to the IAPI, including a logistic regression, decision tree, random forest,[47] artificial neural network (ANN),[48] eXtreme Gradient Boosting algorithm (XGBoost),[49] support vector machine (SVM), k-nearest neighbors (k-NN). Logistic regression is suitable for binary classification problems, while decision trees can handle both binary and multi-class problems. Random forests and XGBoost are based on decision trees and are known for their good performance in predicting both continuous and categorical variables. ANNs can be used for nonlinear problems, but they require more time for training. SVM and k-NN are also popular for classification problems, but they require different preprocessing techniques.

To evaluate the performance of each model, we will be using the cross-validation. With k-fold cross-validation, the data is randomly divided into k subsets, and each model is trained on k-1 subsets and tested on one subset. This process is repeated k times, with each of the k subsets being used once as the test set. The average

performance across all k tests is then used as the final performance measure. To assess the degree of potential over-fitting of each algorithm, we will be trained them using a 10-fold 10-repeat cross-validation procedure.

### *4.2.2 Model assessment*

To evaluate the predictive performance of the developed model, we used the area under the receiver operating characteristics curve (AUC-ROC) to assess discrimination accuracy in the internal validation cohort. The AUC-ROC is an index that measures the classification ability of a model, with a value close to 1 indicating high accuracy and a value close to 0.5 indicating low accuracy. We used three different cutoff points for the IAPI risk score to estimate the levels of progressive PI severity in population-based studies. These cutoff points were used to categorise participants into different risk groups based on their predicted risk of IAPI. We compared all models with Braden scale, Waterlow scale, Norton scale, Cubbin & Jackson scale, and Munro scale. 95% confidence intervals (CIs) were computed using bootstrapping with 2000 random draws.[50] A bootstrap 95% CI was calculated for the AUC-ROC. This allowed us to assess the stability and reliability of the model's predictions. To inspect the calibration of the predictive models, we estimated linear regression models between predicted and observed liver stiffness values using calibration intercepts and slopes. Calibration intercepts represent the average difference between the predicted and observed values, while calibration slopes represent the magnitude of the relationship between the two variables. We also plotted graphical representations, such as calibration plots and

Bland-Altman plots, to visually assess the agreement between the predicted and observed values. These plots help us to identify any biases or trends in the data that may affect the model's performance.

### *4.2.3 Secondary outcome assessment*

The secondary outcome of this study is in-hospital mortality,[9] survival analysis, including Kaplan-Meier analysis and log-rank testing, was used to evaluate the association between IAPI and various patient characteristics. Generalized linear mixed-effects regression analysis with a logit link function and a random effect for country was used to account for possible confounding factors. Odds ratios and 95% confidence intervals were used to present the results. We assumed that the occurrence of in-hospital mortality would be rare, ensuring that odds ratio estimates derived from a case-control design could serve as reliable estimators of relative risk for calculating the IAPI mortality attributable fraction. The following approach was used for attributable fraction calculation for each admission type: the inverted probability weights (IPW) for each patient were calculated, representing the cumulative risk of the patient acquiring IAPI during hospitalization, under a multivariable logistic regression analysis including baseline age, Charlson Comorbidity Index,[51] surgical complications,[39,40] and a time-dependent variable for the occurrence of clinically relevant events. We estimated the association between IAPI occurrence on hospital mortality post operation three months through a mixed logistic regression model weighted by IPW. The delta method was employed to compute the 95% CIs for both the odds ratio and attributable mortality.[52]

We also assessed the incidence and attributable mortality of surgical complications in patients during the same hospitalization by . Additionally, we evaluated the duration of hospital stay and associated costs incurred by patients within this hospitalization period.

### *4.2.4 Methodological considerations*

#### *4.2.4.1 Alternate definition of potential predictor variables case considered.*

Potential predictor variables could be inconsistent in definitions of Norton scale,[16,17] Waterlow scale,[18-20] Braden scale,[21] Cubbin & Jackson scale,[22-24] and Munro scale.[25] The quartiles or dichotomous categories of predictor variables will be used as covariates for a specific patient population, while employing classification homogenization to improve clarity for the assessor. Our objective is to attain increased simplicity and validity in assessment scales.

#### *4.2.4.2 Alternate analysis considered.*

The process of variable selection involves using a recursive feature elimination (RFE) algorithm to identify the most important features in the data.[45] This algorithm has been shown to be effective in developing highly sensitive predictive models, and logistic regression can provide better predictive accuracy.[53] A fitted logistic regression model allows for the derivation of a risk score using a points system.[54] This risk score can be used to predict the likelihood of an event occurring. The flexibility and predictive power of logistic regression make it an attractive choice for this analysis.

## 5. Ethical Considerations

### *5.1 Informed consent process.*

This study was approved by the relevant Institutional Review Boards and informed consent will be obtained (No. PJKT2023-007). All patients and families will provide written informed consent/assent and will have the ability to withdraw at any time without explanation.

### *5.2 Privacy and confidentiality measures.*

The participation of patients and their families in this study poses minimal to negligible risks. Their involvement will not have any negative impact or limitations on receiving additional assessments, investigations, consultations, or management as determined by treating surgeons. The only potential risks lie in the security and privacy of their data, including responses to various questionnaires used for identifying prognosticators for IAPI. Our research personnel will take all necessary and customary measures to ensure data security while maintaining patient privacy and confidentiality.

### *5.3 Potential risks and benefits to participants.*

Participants need to provide personal information, such as name, address, phone number, etc. If this information is not processed and protected, it may be leaked by hackers or other means. As previously mentioned, the only potential risks lie in the security and privacy of their data, including responses to various questionnaires used for identifying prognosticators for IAPI. Research results will be disseminated at

international conferences and in manuscripts to peer-reviewed journals.

## 6. Contributors

Yiyue Zhong, and Fengqiu Gong led the study concept and design, selected outcome measures and involved in writing of the manuscript. Yiyue Zhong wrote the first draft of the manuscript. All authors read, critically revised and approved the final version of the manuscript.

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## 8. Competing interests

None.

## 9. Ethics approval

The study was approved by the institutional review board (IRB No. PJKT2023-007) and conformed to the Official Regulation of Medical Records Management in Medical Institutions with regard to patient data integrity and the principles of the Declaration of

Helsinki.

## 10. Provenance and peer review

Not commissioned; internally peer reviewed.

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