19 Risk assessment and its implications for perioperative cardiac arrest

Richard Armstrong

Iain Moppett

Key findings

- Underscoring of ASA Physical Status was a recurrent issue in both the Activity Survey and case reviews.
- A total of 510 of 717 (71%) adult perioperative cardiac arrest cases lacked a specific or individualised risk score.
- Several surgery-specific scores were underused in the cardiac arrest cohort, particularly for patients with hip fractures.
- Omission of risk scoring was particularly prevalent in patients with a high clinical frailty scale score.
- The primary cause of cardiac arrest on panel review was 'patient factors' in approximately half of cases, reconfirming the need to identify 'high-risk' patients and act accordingly.
- Gaps were highlighted in the preoperative assessment of some patients, particularly around the choice of face-to-face or remote assessment and nurse or anaesthetist led.
- In the Activity Survey, 82% of patients had a predicted postoperative mortality of less than 1%, with 2.8% classified as high risk (5–10% predicted mortality) and 1.7% as very high risk (> 10%). In contrast, 32% of cases who were reported to the Seventh National Audit Project (NAP7) after cardiac arrest had a predicted mortality of less than 1%, with 14.5% high risk and 27.1% very high risk.
- Increasing early mortality risk identified using objective tools is associated with a greatly increased risk of perioperative cardiac arrest. Compared with lowest risk (< 1% predicted risk of early mortality), patients whose risk is judged to be low (1–5%), high (5–10%) and very high (> 10%) have an estimated relative risk of perioperative cardiac arrest of 5.2, 13.3 and 40.9 respectively.
- The absolute risk of perioperative cardiac arrest for patients with Surgical Outcome Risk Tool (SORT)-predicted risk of 30-day mortality of less than 1% is approximately 0.014% (95% confidence interval, CI, 0.013–0.016, 1 in ~7,000) compared with 0.2% (95% CI 0.16–0.23, 1 in ~1,300) for patients with 5–10% predicted risk and 0.6% (95% CI 0.51–0.67, 1 in ~170) for those with greater than 10% predicted risk.

What we already know

Individualised preoperative risk assessment serves many potential purposes, including care planning (eg anaesthetic technique, monitoring, postoperative care, to operate or not), communication (with patients, families, other clinicians, documentation) and benchmarking for the purposes of audit and/or quality improvement. Risk assessment is a central pillar of shared decision making, which is indicated for all surgery but particularly when the risk of intervention increases (CPOC 2021a).

The assessment of risk and communication of this assessment to patients is recommended in the *Guidelines for the Provision of Anaesthetic Services* (RCoA 2023) across a range of clinical domains including general, emergency laparotomy and trauma and orthopaedics. It also forms a key part of the care pathways recommended by the Centre for Perioperative Care for people living with frailty (CPOC 2021a), the Perioperative Quality Improvement Project for patients undergoing major, non-cardiac surgery (RCoA 2021), the Royal College of Surgeons of England for the high-risk general surgical patient (RCSE 2018) and the Centre for Perioperative Care guideline *Preoperative Assessment and Optimisation for Adult Surgery* (CPOC 2021b). Specific recommendations also exist regarding the appropriate location for postoperative care of patients identified as being at increased perioperative risk (RCSE 2018, RCoA 2021, FICM 2020). There is good evidence that these scores provide reasonable estimates of early mortality risk. However, they generally provide little information about other outcomes of importance to patients, such as those provided by the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) Surgical Risk Calculator (https://riskcalculator.facs.org).

Risk scoring is now recommended in clinical guidelines for all patients undergoing surgery (CPOC 2021b) and is mandated both in the NHS recovery plan (NHSE 2022) and, in England, in its NHS standard contract (NHSE 2023). Risk assessment tools may be generic (eg ASA Physical Status, SORT, P-POSSUM, ACS-NSQIP) or specific to clinical specialties or procedures (eg National Emergency Laparotomy Audit, Nottingham Hip Fracture Score, Euroscore, Thoracoscore). Some risk scores (eg SORT-2, ACS-NSQIP) include an adjustment that factors in clinician judgement and this may improve performance (Wong 2020). These measures describe outcomes for populations rather than individuals and are perhaps better described as likelihood tools. It has often been argued they should not be used for individual risk allocation: risk tools often lack the granularity to account for variation in individual risk (eg unmeasured patient factors or factors specific to the individual healthcare setting), which may alter their validity (discrimination) and may also lack consistency in predicting the correct outcome (calibration; Mathiszig-Lee 2022, Lee 2023) meaning that application to individuals is hazardous. It is unclear how widely, and for what purposes, these scores are used in routine clinical practice.

What we found

Issues relating to risk assessment or scoring were highlighted by the review panel for 101 cases (11.5%). These cases tended to have higher frailty scores than the Activity Survey denominator population and were also older on average than both the Activity Survey group (median 70.5 years, IQR 60.5–80.5 vs 52.8 years, IQR 32.1–69.2) and the rest of the cardiac arrest cohort (median 60.5 years, IQR 40.5–80). In this group of patients, the most common panel-agreed key cause of cardiac arrest was patient factors, mirroring the cardiac arrest cohort as a whole. Care before cardiac arrest was rated 'good' in 32 (32% compared with 48% of all cases), with elements of poor care identified in 40 (40%, 32% of all cases). The specific causes of cardiac arrest and mix of clinical specialties were similar to the wider cardiac arrest cohort. Ratings of other aspects of care from full panel review were similar in this case group to the entire cohort, including appropriate numbers and seniority of anaesthetists, location of anaesthesia care, anaesthesia techniques and monitoring used.

In the Activity Survey, there was an inconsistent association between consultant involvement and ASA (as a crude surrogate for risk): ASA 1–2 70%, ASA 3 79%, ASA 4 82% and ASA 5 63%. For cardiac arrest cases, a more consistent association of consultant presence at induction of anaesthesia and ASA Physical Status was seen: ASA 1–2 74%, ASA 3 85%, ASA 4 87% and ASA 5 88%.

Underscoring of ASA grade

The ASA Physical Status Classification System (ASA 2020) includes specific examples. This enables an objective measure of the accuracy of ASA classification for certain patient groups. In the Activity Survey, we examined specific comorbidities, as well as body mass index (BMI) and pregnancy, and found high rates of under-scoring. The yellow highlighted boxes in Table 19.1 show how patients were under-scored according to the ASA specification (eg for cerebrovascular disease the ASA class should be at least 3, so those scored 2 are under-scored). Cardiovascular comorbidities were particularly commonly under-scored; for example, 66% of those with severe aortic stenosis and more than 50% of those with a previous myocardial infarction (MI) or acute coronary syndrome (ACS) within three months or New York Heart Association class III/IV congestive cardiac failure (all ASA 4+ by definition) were under-scored.

Table 19.1 ASA Physical Status classification for specific comorbidities in the Activity Survey. The yellow boxes indicate numbers of under-scored patients. ACS, acute coronary syndrome; CVA, cerebrovascular accident; MI, myocardial infarction; NYHA, New York Heart Association Functional Classification; TIA, transient ischaemic attack.

Comorbidity	ASA					Under scored (%)
	1	2	3	4 to 6	Total	
Cerebrovascular disease (TIA/CVA)	0	152	502	148	802	19.0
MI or ACS within 3 months	0	6	39	37	82	54.9
MI or ACS older than 3 months	0	119	451	119	689	17.3
Severe aortic stenosis	0	4	64	35	103	66.0
Congestive cardiac failure (NYHA III/IV)	0	4	135	127	266	52.3
Permanent pacemaker	0	26	143	55	224	11.6
Implantable cardioverter defibrillator	0	4	29	24	57	7.0
Chronic kidney disease grade 5 (dialysis dependent)	0	5	108	49	162	3.1
Body mass index (kg m^{-2})						
≥ 30 to < 40	451	3168	1444	209	5272	8.6
≥ 40	23	368	580	49	1020	38.3

BMI was incorrectly interpreted, with more than one-third of those with obesity class III (BMI > 40 kg m^{-2}) under-scored (minimum ASA 3 by definition). Uncomplicated pregnancy is ASA 2 by definition, so any patients classed ASA 1 are under-scored. We found this to be the case for around 25% of cases (Table 19.2).

Table 19.2 ASA Physical Status classification for obstetric patients in the Activity Survey

Procedure	ASA 1	Total	Under scored (%)
Caesarean section	338	1681	20.1
Labour analgesia	275	1010	27.2
Other	129	485	26.6
All	742	3146	23.6

The same issue was present in the cardiac arrest case reports, although to a lesser extent. For the same specific examples given above, most were scored appropriately, with severe aortic stenosis and presence of a permanent pacemaker the most commonly under-scored (Table 19.3). Only 14% of obstetric patients were classed ASA 1. However, these examples are a limited sample of potential inconsistencies with ASA classification. On panel review of NAP7 case reports, under scoring of ASA was specifically highlighted in 36 (4%) cases, commonly due to the presence of acute illness (eg sepsis) appearing not to be taken into consideration in determining ASA.

Lack of individualised risk assessment

In addition to recording the ASA Physical Status class, the NAP7 registry included a specific question about individualised risk assessment, asking whether this was undertaken, and if so, which tool had been used. Among 717 reports of adult cardiac arrests, 510 (71%) did not record use of an individualised risk assessment. Of those that did, most (123, 59% of risk assessments and 17% of all adult cases) had a quantitative risk score calculated (eg SORT, NELA) rather than a qualitative assessment. The outcome of the risk assessment was reported for 186 cases, two-thirds of which were classified as high or very high risk (Table 19.4). Twenty-one per cent of cases which underwent full panel review were deemed to lack an appropriate risk score, most commonly a hip fracture specific score (eg Nottingham Hip Fracture score) for orthopaedic trauma cases.

A patient aged over 85 years with frailty and an active 'do not attempt cardiopulmonary resuscitation' (DNACPR) recommendation underwent hemiarthroplasty for a hip fracture. The ASA Physical Status class was reported as 2, despite previous myocardial infarction, and no individualised risk assessment was reported. Invasive blood pressure monitoring was not used. The patient had a spinal anaesthetic. There was loss of cardiac output following cementing and resuscitation efforts were stopped after 10–20 minutes.

Table 19.4 Mortality associated with reported and estimated risk calculation of individualised risk assessment (qualitative or quantitative) and patient mortality at time of NAP7 reporting. The final column covers an estimated SORT score for all cases. Values are number (proportion).

Estimated risk of early mortality	Cases, *n* (%)	Observed in-hospital mortality (cases with risk score reported), *n* (%)	Observed in-hospital mortality (all cases), *n* (%)
Not estimated/ reported	531 (74)	206/531 (39)	–
< 1%	13 (2)	3/13 (23)	31/229 (14)
Low (< 5%)	47 (7)	16/47 (34)	69/188 (37)
High (5–10%)	43 (6)	15/43 (35)	59/104 (57)
Very high (> 10%)	83 (12)	59/83 (71)	139/194 (72)

Table 19.3 ASA Physical Status classification for specific comorbidities in NAP7 case reports. NYHA, New York Heart Association Functional Classification.

Comorbidity	ASA						Under scored (%)
	1	2	3	4	5	Total	
Cerebrovascular disease	0	1	13	12	4	30	3.3
Myocardial infarction	0	3	37	22	8	70	4.3
Severe aortic stenosis	0	0	7	9	0	16	43.8
Congestive cardiac failure (NYHA III/IV)	0	0	9	25	1	35	25.7
Permanent pacemaker	0	0	8	9	2	19	42.1
Chronic kidney disease grade 5 (dialysis dependent)	0	1	9	16	1	27	3.7
Body mass index (kg m^{-2})							
≥ 30 to < 40	1	47	83	46	8	185	0.5
≥ 40	0	8	14	17	2	41	19.5

The cases submitted represent a higher-risk cohort than those in the Activity Survey, which would support the need for individualised risk assessment. A SORT score can be estimated for cases reported to the registry as well as the Activity Survey population. For the purpose of this calculation, we included adult non-obstetric patients with all SORT data items complete (specialty, grade and urgency of surgery; ASA class; presence or absence of malignancy; age). The age categories of NAP7 do not align exactly with those of the SORT score so those aged 76–85 years were scored as if they were all 65–79 years, which will result in an underestimate for a proportion of patients.

In the Activity Survey, the large majority of patients (82%) had a predicted postoperative mortality of 1% or less, with 2.8% classified as high risk (5–10% predicted mortality) and 1.7% as very high risk (> 10%). In contrast, 32% of cases who were reported to NAP7 after cardiac arrest had a predicted mortality 1% or less, with 14.5% high risk and 27.1% very high risk (Figure 19.1).

The absolute risk of perioperative cardiac arrest for patients with SORT-predicted risk of 30-day mortality of less than 1% is approximately 0.014% (95% CI 0.013–0.016, 1 in ~7000) compared with 0.2% (95% CI 0.16–0.23, 1 in ~1,300) for patients with 5–10% predicted risk and 0.6% (95% CI 0.51–0.67; 1 in ~170) for those with greater than 10% predicted risk. The relative risk of a perioperative cardiac arrest compared with those at low SORT risk (< 1%) is 5.2 (95% CI 4.3–6.3) for those with 1–5% predicted risk, 13.3 (95% CI 10.6–16.8) for those with 5–10% predicted risk and 40.9 (95% CI 33.8–49.5) for those with greater than 10% risk (Table 19.5).

Figure 19.1 Cumulative distribution of estimated SORT scores in NAP7 Activity Survey (purple line) and cardiac arrest case registry populations (blue line). Dotted line shows 5% risk, green line shows 1% risk, conventionally the distinction between low and high risk of mortality.

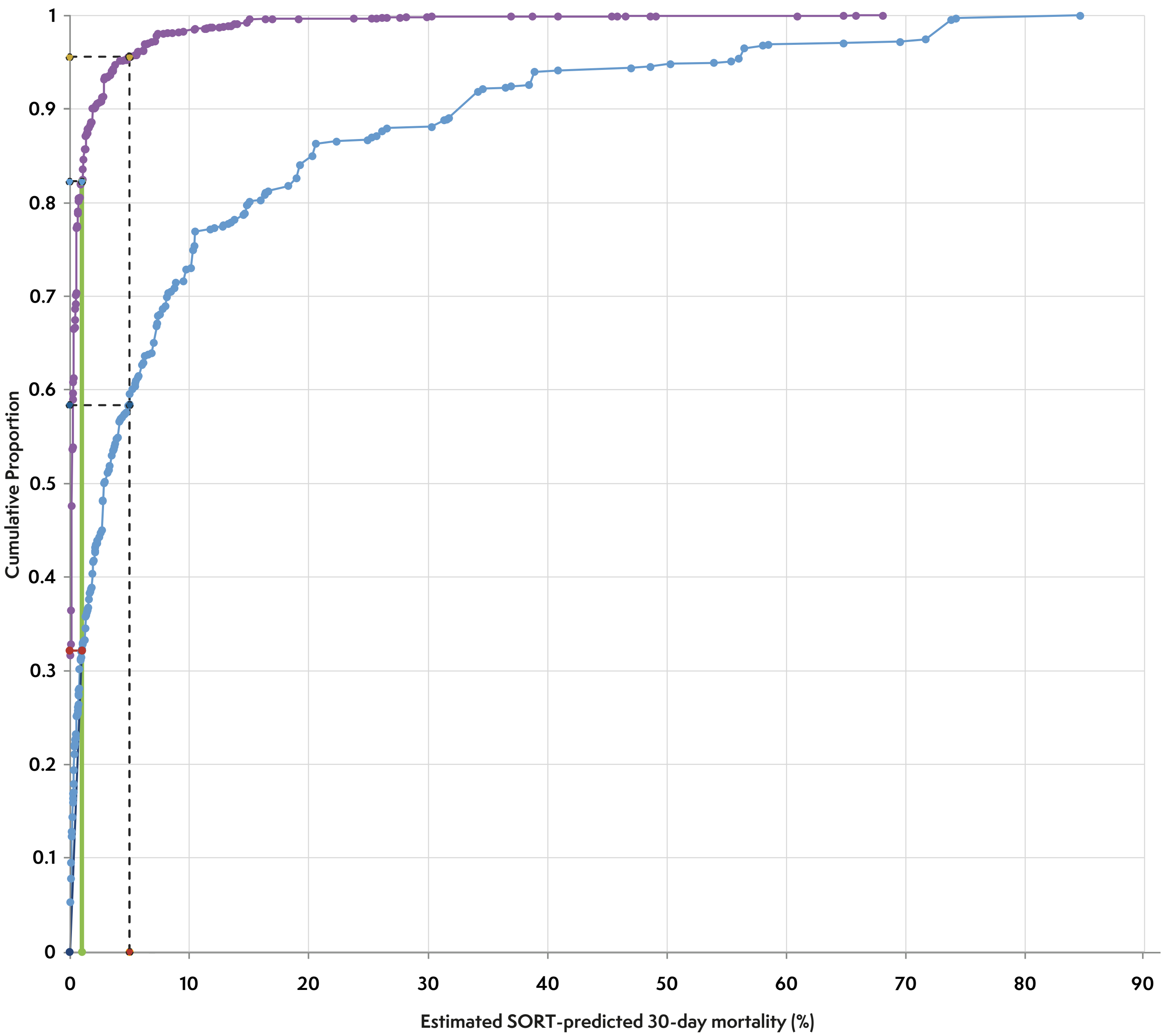

Table 19.5 Risks of cardiac arrest associated with estimated early mortality risk using the SORT score in adult, non-obstetric patients (*n* = 17,567). Values are number (proportion) or estimate (95% confidence interval, CI). Details of the multiplication factor to estimate the annual case numbers is given in Chapter 11 Activity Survey. RR, relative risk.

Estimated risk of early mortality (SORT) (%)	Activity Survey denominator, *n* (%)	Estimated annual cases (*n*)	Reported cases (*n*)	Incidence (%)	1 in x (95% CI)	RR vs low-risk group (95% CI)
< 1%	14,176 (82)	1,607,230	229	0.014 (0.013–0.016)	1 in 7,018 (6173–8000)	1 (reference)
1–5%	2,303 (13)	254,805	188	0.074 (0.064–0.085)	1 in 1,355 (1172–1567)	5.2 (4.3–6.3)
5–10%	476 (2.8)	54,881	104	0.19 (0.16–0.23)	1 in 528 (433–641)	13.3 (10.6–16.8)
> 10%	289 (1.7)	33,321	194	0.58 (0.51–0.67)	1 in 172 (149–198)	40.9 (33.8–49.5)

Preoperative assessment issues

Of cases that underwent full panel review, 83% were judged as having appropriate preoperative assessment, appropriate preoperative investigations ordered and results noted. For those in which issues were identified, a common theme was the omission of preoperative investigations, particularly ECG, which the panel judged should have been performed and/or which would be recommended under National Institute for Heath and Care Excellence guidance on preoperative testing (NICE 2016). There were also cases that had nurse-led preoperative assessment, but the panel (and in some cases the reporter) judged that an anaesthetist-led assessment would have been more appropriate, and several in which remote preoperative assessment was considered to have failed to identify issues that an in-person assessment would have highlighted.

A middle-aged patient with a BMI greater than 40 kg m^{-2} had a telephone preoperative assessment with a nurse before a major elective procedure. The patient was under-scored as ASA 2 and a history of obstructive sleep apnoea with home CPAP (continuous positive airway pressure) was not elicited by the preassessment or by the anaesthetist on the day of surgery. The patient received opioids as part of their anaesthetic and had a respiratory arrest on the ward postoperatively.

Decision making

There were cases in which the panel judged that, given the data available before surgery and anaesthesia, operating may not have been in the patient's best interests. By definition, the reported cases do not include patients where a decision not to offer or proceed with surgery was made following risk assessment, nor those where cardiac arrest did not occur within 24 hours, but outcomes were poor. It is therefore impossible for the panel to comment on whether proceeding to surgery inappropriately is a rare or common occurrence, but it clearly does occur.

An older patient with moderately severe disability, severe frailty, advanced dementia and a solid-organ malignancy was listed for an intramedullary nail under a consent form 4. They were anaemic and hypoxic preoperatively. No treatment plans or DNACPR recommendations were in place. The patient had a cardiac arrest during the procedure under spinal with sedation. The procedure was abandoned and the patient was transferred to ICU intubated and ventilated for continuing care.

Discussion

We identified issues related to a lack of individualised risk assessment, frequent omission of relevant quantitative risk scoring tools, under-scoring of ASA Physical Status and gaps in preoperative assessment. As expected, we also found that the cardiac arrest population were a high-risk group relative to the Activity Survey population.

The most widely used tool is ASA Physical Status, which is ubiquitous in clinical practice. We found widespread under-scoring of ASA class based on published examples, particularly in the Activity Survey data. Common pitfalls related to specific comorbidities that attract a higher ASA class (especially cardiovascular), BMI categories and the fact that uncomplicated pregnancy is classed as ASA 2 (ASA 2020). An issue that was particularly apparent on panel review of submitted cases was a failure to increase ASA class on the basis of acute illness (eg sepsis and shock are ASA 4 according to the published examples and ruptured abdominal aortic aneurysm and massive trauma are ASA 5; ASA 2020). Outstanding issues include how to deal with the inherent subjectivity of the ASA system, and the extent to which frailty should be incorporated into the ASA Physical Status assigned to an individual compared with its use as a separate standalone indicator. ASA alone is not designed or validated for risk assessment. However, it does form part of numerous assessment tools. Consistency in its application is therefore important. The distinction between 'mild' (ASA 2) and 'severe'

(ASA 3) systemic disease is particularly problematic, with many patients who are not covered by specific examples falling into this 'ASA 2.5' gap. Some of these inconsistencies probably carry little implication for direct patient care – whether a pregnant woman undergoing caesarean section is classified as ASA 1 or 2 is not going to change practice, but if data are to be compared across time or between units, then consistency is important.

Risk tools have important roles in risk stratifying, consideration of alternatives to planned interventions and in planning postoperative pathways. They should not be used in isolation, but should be integrated with other site specific and patient specific information (Lee 2023). While their use is recommended in guidance from multiple sources (RCSE 2018; FICM 2020; CPOC 2021a, 2021b, RCoA 2021, 2023) there appears to be a gap in their implementation in routine practice. Potential reasons for this include a belief in 'self-assessment', which is prone to issues of bias and a lack of follow-up, a lack of observable change by patients or system in response to high- or low-risk values, evident flaws with all tools (unusual but significant prognostic indicators are not usually included in model development) leading to lack of confidence, and a lack of easy access to tools.

Quantitative tools are important, as they enable an estimated risk to be communicated to the patient, facilitating shared decision making and informed consent, and across the multidisciplinary team. The communication of risk or likelihood of an outcome to an individual patient needs to be managed carefully if it is not to add confusion. Most tools simply predict the likelihood of a dichotomised outcome (generally death). While a population may have a risk of 10% mortality (1 in 10 of the patients will die), for each patient the outcome is absolute: each patient undergoing surgery will either survive or die, and for them the outcome happens with an incidence of 100% or 0%. For some patients, surgery is a part of a palliative care process, and should not be denied simply because the risk of death is high. It is important to understand the risks associated with not operating (McIlveen 2019) and be mindful that risk assessments usually refer to the 30-day mortality – the daily rate of death is much lower (Johansen 2017). Although there is a clear association between higher risk (whether assessed by broader methods such as ASA or more specific methods such as SORT) and the risk of cardiac arrest, the absolute risks of cardiac arrest remain low. However, risk assessment provides an opportunity for the perioperative team and the patient and their family to consider the purpose, risks and benefits of planned procedures.

NAP7 helps to demonstrate the potential value of widely available tools such as the SORT score in identifying high-risk patients who might benefit from adjustments to care pathways. While not every patient suffering a perioperative cardiac arrest would be classified as high risk, more consistent application of these tools can aid informed consent and shared decision making while streamlining clear communication across the perioperative team.

Recommendations

National

- National bodies such as regulators and royal colleges should include evaluation of appropriate discussion and documentation of quantitative risk assessment in their assessments of organisations.

Institutional

- Organisations should provide mechanisms that facilitate the use of validated risk assessment tools in their patient records.
- Risk scoring, using validated tools, should be a routine part of preoperative assessment and shared-decision making. It should be considered both before and after a procedure to ensure patients receive the appropriate level of post-operative care.
- Organisations should explore whether quantified risk scoring and ASA Physical Status can be safely incorporated as forced data for booking of emergency patients.

Individual

- Anaesthetists should apply ASA classification in line with updates and current recommendations.
- Anaesthetists should, in collaboration with other colleagues, include objective risk assessment as part of prelist briefings.
- As part of early preoperative information provision, patients should be provided with a realistic assessment of likely outcomes of their treatment. The information provided should routinely include important risks, including the risk of death during anaesthesia and surgery.

Research

- Research is needed on the impact of quantitative risk assessment on:
  - patient decision making
  - perioperative clinical decision making.

References

ASA 2020: American Society of Anesthesiologists. ASA Physical Status Classification System. https://www.asahq.org/standards-and-guidelines/asa-physical-status-classification-system. (Accessed 20 September 2023).

CPOC 2021a: Centre for Perioperative Care. *Guideline for Perioperative Care for People Living with Frailty Undergoing Elective and Emergency Surgery*. London: Centre for Perioperative Care; 2021. https://cpoc.org.uk/guidelines-resources-guidelines/perioperative-care-people-living-frailty (accessed 20 September 2023).

CPOC 2021b: Centre for Perioperative Care. *Preoperative Assessment and Optimisation for Adult Surgery including consideration of COVID-19 and its implications*. London: Centre for Perioperative Care; 2021. https://www.cpoc.org.uk/preoperative-assessment-and-optimisation-adult-surgery (accessed 20 September 2023).

FICM 2020: Faculty of Intensive Care Medicine. *Enhanced Care: Guidance on service development in the hospital setting*. London: Faculty of Intensive Care Medicine; 2020. https://www.ficm.ac.uk/standardssafetyguidelinescriticalfutures/enhanced-care (accessed 20 September 2023).

Johansen 2017: Johansen A, Tsang C, Boulton C, Wakeman R, Moppett I. Understanding mortality rates after hip fracture repair using ASA physical status in the National Hip Fracture Database. *Anaesthesia* 2017; 72: 961–6.

Lee 2023: Lee A, Moonesinghe SR. When (not) to apply clinical risk prediction models to improve patient care. *Anaesthesia* 2023; 78: 547–50.

Mathiszig-Lee 2022: Mathiszig-Lee JF, Catling FJR, Moonesinghe SR, Brett SJ. Highlighting uncertainty in clinical risk prediction using a model of emergency laparotomy mortality risk. *Nature Digital Med* 2022; 5: 70.

McIlveen 2020: McIlveen EC, Wright E, Shaw M, *et al* A prospective cohort study characterising patients declined emergency laparotomy: survival in the 'NoLap' population. *Anaesthesia* 2020; 75: 54–62.

NHSE 2022: NHS England. *Delivery Plan for Tackling the COVID-19 Backlog of Elective Care*. London: NHS England; 2022. https://www.england.nhs.uk/coronavirus/publication/delivery-plan-for-tackling-the-covid-19-backlog-of-elective-care (accessed 20 September 2023).

NHSE 2023: NHS England. 2023/34 NHS Standard Contract. https://www.england.nhs.uk/nhs-standard-contract/23-24/ (accessed 20 September 2023).

NICE 2016: National Institute for Health and Care Excellence. Routine Preoperative Tests for Elective Surgery. NICE Guideline NG45. London: National Institute for Health and Care Excellence; 2016. https://www.nice.org.uk/guidance/ng45 (accessed 20 September 2023).

RCoA 2021: Royal College of Anaesthetists. Perioperative Quality Improvement Programme Report 3: August 2019 – July 2021. https://pqip.org.uk/FilesUploaded/PQIP-Annual-Report_2021.pdf (accessed 20 September 2023).

RCoA 2023: Royal College of Anaesthetists. *Guidelines for the Provision of Anaesthetic Services*. London: RCoA; 2023. https://rcoa.ac.uk/safety-standards-quality/guidance-resources/guidelines-provision-anaesthetic-services (accessed 20 September 2023).

RCSE 2018: Royal College of Surgeons of England. *The High-Risk General Surgical Patient: Raising the standard*. London: RCS and Department of Health; 2018. https://www.rcseng.ac.uk/library-and-publications/rcs-publications/docs/the-higher-risk-general-surgical-patient (accessed 20 September 2023).

Wong 2020: Wong DJN, Harris S, Sahni A *et al* Developing and validating subjective and objective risk-assessment measures for predicting mortality after major surgery: An international prospective cohort study. *PLoS Med* 2020; 17: e1003253.