

Better approach to optimize perioperative care for high risk older patients undergoing non cardiac surgeries: A narrative review

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REVIEW

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ABSTRACT

Background

As the population is aging, an associated rise in comorbidities augment perioperative mortality and morbidity. Evidence is emerging to improve perioperative care for high-risk patients in view of better postoperative outcomes.

Aims

While there are number of international guidelines describing preoperative evaluation of such patients, a comprehensive review of a high-risk older patient's journey through non-cardiac surgery is lacking in the literature. The aim of this review is to recapitulate current evidence for management approaches of high-risk patients undergoing non-cardiac surgeries.

Methods

In this review, literature search was conducted through East Metropolitan Health library service for studies and guidelines published on high risk older patients undergoing non cardiac surgeries. Priority was given to the evidence on preoperative risk stratification, investigation and management of chronic medical conditions and postoperative care.

Conclusion

The available evidence should be used to optimize perioperative outcomes of high and intermediate risk older patients undergoing non-cardiac surgeries.

Key Words

High risk, perioperative, noncardiac surgery, risk stratification

What this review adds:

1. What is known about this subject?

Operative procedures in high-risk older patients increase morbidity and mortality significantly. Current evidences are limited on proper risk stratification, optimizing medical comorbidities and post-operative care of those patients to minimize perioperative complications.

2. What new information is offered in this review?

This review article offered comprehensive summary of available evidences to re-engineer older high-risk patients' journey through surgical procedures.

3. What are the implications for research, policy, or practice?

Further large-scale randomized studies are required to develop better pathways and guidelines to improve outcomes of high-risk patients journeying through NCS.

Introduction

Annually, approximately 234.2 million major surgeries are performed worldwide, equating to one per 25 people.¹ In Australia, 662,000 patients underwent elective surgeries in public hospitals in 2011. The majority of these were non cardiac surgeries (NCS), with cardiac surgeries accounting for fewer than 20 per cent.² Patients undergoing non-cardiac procedures carry an increased risk of major cardiovascular complications including acute coronary events, heart failure, arrhythmia or stroke.^{3,4} The National Surgical Quality Improvement Programme (NSQIP) found an average thirty-day mortality of 3.5 per cent to 6.9 per cent

in patients undergoing vascular and general surgeries.⁵ Patients with underlying cardio-respiratory disease carry an increased risk of morbidity and mortality. Mcnicole, et al demonstrated a 6 per cent thirty-day mortality in patients with increasing age, more co-morbidities and low albumin undergoing NCS.⁶ Hip fracture data evaluating 8930 patients revealed that cardiac and pulmonary complications are of similar incidence (2 per cent and 3 per cent respectively).⁷

Multiple studies have been performed on perioperative care of high-risk older patients undergoing NCS. Additionally, several international guidelines exist in prevention of potential complications in patients with cardio-respiratory disease undergoing NCS.⁸⁻¹⁰ The aim of this article is to evaluate those guidelines and other available data to outline an approach to improve peri-operative care in such patients going through NCS. In this review, a literature search was done through East Metropolitan Health library service for studies published on high risk older patient care during the peri-operative period.

Peri-operative clinic and pre-op care

Patients with cardiac or respiratory disease referred for NCS should be identified as high-risk surgical candidates by the relevant surgical clinic. Those who have an intermediate or high risk of adverse outcomes should be referred to a pre-operative clinic for further evaluation. Pre-operative clinics have shown improved surgical outcomes and advanced patient focused management planning.¹¹ Pre-operative evaluation and optimization of cardiac and respiratory co-morbidities will be carried out in pre-operative clinics according to the following layout.

Cardio-respiratory risk stratification

Clinical assessment:

All patients undergoing elective non-cardiac procedures with known cardio-respiratory diseases should be reviewed thoroughly. This includes history taking, bedside examination, investigations and evaluation of past medical issues. The assessment takes place in a pre-operative clinic by a peri-operative medicine trained physician with good communication with the anaesthetist and surgeon involved. There are various tools to assess the risk of peri-operative adverse outcomes. Amongst them, the Revised Cardiac Risk Index (RCRI) is a well validated tool for assessment of major cardiac complications described by Goldman et al.¹² The RCRI, combined with surgical risk, is a good predictor of peri-operative mortality and major cardiac adverse events (Table 1).

Table 1: Revised Cardiac Risk Index (RCRI)¹²

Variable	Point
High-risk type of surgery (see table 3)	1
Ischaemic heart disease	1
History of congestive heart failure	1
History of cerebrovascular disease	1
Preoperative treatment with insulin	1
Preoperative serum creatinine level >177µmol/L	1

An RCRI of 3 or more indicates a high risk of major cardiac complications.¹³ Further details of risk categorization according to the RCRI score is shown in Table 2.

Table 2: Interpretation of RCRI score¹³

Risk class	Points	Risk of complications
Low	1	0.9%
Moderate	2	7.0%
High	3+	11.0%

The NSQIP risk calculator is another risk stratification tool, developed by the American College of Surgeons National Surgical Quality Improvement Program.⁵ The NSQIP calculator predicts complication risk as well as patient centred outcomes such as discharge destination (for example, home vs. nursing home).

Risk factors for pulmonary complications after NCS could be patient related factors such as advanced age, smoking, American Society of Anaesthesiologists (ASA) class, chronic obstructive airway disease (COPD) / asthma, heart failure, obstructive sleep apnoea, pulmonary hypertension. Procedure related factors also increase pulmonary complication risk including aortic aneurysm repair, general anaesthesia and prolonged or emergency surgeries. Furthermore, some surgeries (abdominal, neurological, head and neck, vascular) carry greater incidences of pre- and post-operative pulmonary complications.^{14,15} There are several pulmonary risk calculators in clinical practise to predict post-operative adverse respiratory outcomes. Carnet et al described the ARISCAT score based on seven factors and it is well validated in predicting post-operative pulmonary complications.¹⁶ The Arozullah respiratory failure index¹⁷ and Gupta calculator¹⁸ are some of other pulmonary risk stratification tools.

Functional assessment:

Self-reported exercise tolerance is a poor predictor of true

functional capacity in the pre-operative setting.¹⁹ Rather, a scoring system such as The Dukes Activity Status Index (DASI) which has been shown to have good clinical implication, should be used. The DASI provides a score from 0–58 based on a structured questionnaire and estimates peak oxygen uptake. A calculated value of 12.75 is equivalent to four metabolic equivalents (METs).²⁰ A MET is the ratio of energy a person expends relative to their body mass. One MET is 3.5mlO₂/kg/min and equals the amount of oxygen consumed at rest by a 40-year-old male weighing 70kg. Climbing two flights of stairs is approximately 4METs. Patients with a capacity of less than 4METs carry high peri-operative risk for adverse cardiac events.¹⁹

Surgery categorization:

Surgical procedures are divided into three categories according to the severity of the surgical stress response²¹ (Table 3). Surgical stress largely depends on extent and duration of the procedure which is known to increase risk of cardiac ischaemia. Low-risk surgeries carry less than 1 per cent of adverse outcome risk and it will be more than 5 per cent in high-risk categories.

Table 3: Risk categorization of common surgeries²¹

Low risk (< 1%)	Intermediate risk (1%–5%)	High risk (>5%)
Breast	Abdominal	Aortic and major
Dental	Carotid	Vascular
Endocrine	Peripheral arterial angioplasty	Peripheral vascular
Eye	Endovascular aneurysm repair	
Gynaecological	Head and neck	
Plastic	Neurological or orthopaedic	
Orthopaedic – minor	— major (hip and spine)	
Urological - minor	Lung, renal or liver transplant	
	Urological — major	

Further Investigations

Patients at increased cardiovascular risk with poor functional status and undergoing intermediate or high-risk surgeries will qualify to have further cardiac investigations and assessments in the peri-operative clinic.

Trans-thoracic echocardiogram (TTE):

TTE is a non-invasive cardiac test which provides valuable information regarding cardiac function and valvular pathology. However, there is limited evidence of benefit

performing resting TTE in a peri-operative setting unless there is a clear indication to do so, such as valvular pathology or evidence of systolic impairment.²² There was no improvement of mortality or hospital length of stay associated with performing TTE prior to NCS.²³

Cardio Pulmonary Exercise Testing (CPET):

CPET is an assessment of physiological response to exercise or stress. Serial measurements of heart rate, minute ventilation, blood pressure, oxygen saturation and electrocardiogram are used to calculate cardio-pulmonary capacity and reserve. Although CPET provides prognostic value in cardiac patients, there is no clear outcome benefit of routine use in most of the literature.²⁴ However, there was some value of anaerobic threshold in predicting cardiovascular mortality.^{25,26}

Stress testing:

Stress Electrocardiogram (ECG) or Stress TTE is indicated in high risk patients (patients with RCRI ≥3) to evaluate risk of peri-operative cardiac events.^{27,28} Stress TTE can identify early perfusion defects which are predictive of post-operative adverse cardiac events.²⁹

Myocardial Perfusion Scan (MPS):

Patients with intermediate vascular risk appeared to benefit from dipiridamole thallium MPS, in predicting adverse outcomes after surgeries.²⁹ But low and high risk patients did not gain additional benefit from MPS compared to clinical risk assessment.³⁰ Pre-operative MPS also demonstrated prognostic information on long term event-free survival benefit in vascular surgeries.^{31,32} However, the cost effectiveness of MPS compared to clinical risk stratification in predicting myocardial injury in NCS is controversial.³³

Biomarkers:

Serum Troponin (traditional or high sensitive), a preferred marker for acute coronary events, demonstrated close association with postoperative adverse cardiac events.³⁴ BNP and NT-proBNP which are released when there is myocardial stress or damage have prognostic value in cardiovascular risk stratification.³⁵ BNP levels of ≥92ng/L or NT-proBNP levels of ≥300ng/L are very strong predictors of postoperative mortality or cardiac morbidity.³⁶

Lung function tests:

Spirometry is freely available and relatively inexpensive to perform. However, its predictive value of peri-operative pulmonary complications is limited.³⁷ Indications to perform the test for pre-operative assessment are lung resection,

cardiac bypass, unexplained dyspnoea and uncontrolled asthma/chronic obstructive airway disease (COPD) where the baseline is uncertain.

Prophylactic treatments

Patients with cardiovascular risk factors who are on primary or secondary prophylactic treatments should be continued during the peri-operative period for as long as possible.

Beta Blockers (BBs):

Beta Blockers are mainstay in management of acute coronary syndrome. BBs minimize myocardial oxygen demand by slowing heart rate and contractility. Additional benefits include coronary plaque stabilization and reduced vascular inflammation.

Large randomized trials, including the Peri-operative Ischemia Evaluation (POISE) study demonstrated benefits of extended-release Metoprolol commenced 2–4 days pre-operatively and continued for 30 days post-operatively. This prevented 15/1000 myocardial infarctions. However, an increased risk of stroke, hypotension, bradycardia and higher incidence of mortality was reported in those who were given Metoprolol.³⁸ The main criticism was late initiation of BBs in this study which would have caused the above-mentioned adverse effects. The Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE) trial favoured the use of BBs in the peri-operative setting. However, the study has been side-lined due to misconduct.³⁹ The American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend continuing BBs during the peri-operative period for those who are already on them for longer period of time.⁸ Bisoprolol is the preferred choice among all BBs in optimizing cardiac function.⁴⁰

Aspirin:

Aspirin irreversibly blocks platelet thromboxane A₂ and inhibit platelet aggregation as well as having other effects such as anti-inflammatory and antipyretic properties. Aspirin reduces thrombosis risk in high-risk vascular patients but invariably increases peri-operative bleeding risk. Discontinuing Aspirin in known cardiac patients increases thrombosis risk more than reducing bleeding risk after most surgeries.³² However, the Perioperative Ischemia Evaluation–2 (POISE -2) trial data did not support improvement in mortality with new Aspirin exposure.⁴¹ In fact, it increased major bleeding risk which enhanced incidence of peri-operative MI. There was some criticism of the patient selection of this study as the majority of Aspirin users were not requiring Aspirin as primary or secondary

cardiac prevention.

Current ACC/AHA 2014 guidelines do not recommend initiation or continuation of Aspirin in patients who do not require primary or secondary prevention of coronary events and or when undergoing closed space procedures (intracranial, intramedullary, intraocular, middle ear and prostate). In such situations, Aspirin should be discontinued 5–10 days pre-operatively and restarted as early as possible after the operation. The short-term discontinuation is not associated with increased thromboembolic events.^{42,43} In patients with recent stents or PCI, Aspirin and antiplatelet recommendations will be discussed in the Coronary Revascularization section (5.5).

Statins:

Statins reduce serum cholesterol by inhibiting HMG-coenzyme A reductase and also minimize vascular inflammation, stabilize plaques and dilate coronary vessels. As a result, statins improve mortality and prevent cardiovascular complications in patients with higher cardiovascular risk.^{44,45}

The current recommendation is to continue statins in patients who are already on statin therapy. Peri-operative initiation is reasonable for those undergoing vascular surgeries. Statins with long-acting, extended-release preparations are preferred.⁸

ACEI/ARB:

Angiotensin-Converting Enzyme Inhibitors (ACEI) and Angiotensin Receptor Blockers (ARB) block angiotensin, which is a vasoconstrictor. ACEI/ARB is a first line antihypertensive and a treatment choice for left ventricular systolic failure. It also has nephroprotective properties. Continuing ACEI/ARB increases risk of hypotension and myocardial injury intra-operatively but does not significantly increase post-operative complication risk.⁴⁶ The lack of large randomized studies in this area limits definitive evidence with regards to ACEI/ARB treatments during the peri-operative period but low-quality evidence support withholding them 24hs prior to NCS.

Coronary revascularization:

Coronary revascularization includes percutaneous coronary intervention (PCI), coronary stenting and coronary artery bypass graft (CABG). Prophylactic revascularization failed to demonstrate benefit in patients who are haemodynamically stable.⁴⁷ Management plan for ACS in peri-operative setting does not differ to standard guideline directed therapy in non-surgical patients with acute cardiac events. Antiplatelet

requirements depend on the type of coronary intervention and recommendations of post-stenting antiplatelet therapy are significantly supported by expert opinion.⁴⁸ The current practice of minimum dual antiplatelet therapy duration is 4–6 weeks for bare metal stents (BMS) and 6 months for newer generation drug eluting stents (DES) with 12 months for conventional DES.⁸ However, after an acute coronary event there is an elevated risk for adverse events form NCS. The ACC/AHA recommendation is to allow at least 60 days to elapse before an elective NCS is performed after myocardial injury.⁸

Oxygen:

Maintaining adequate blood oxygen levels is vital to maintain organ function during the perioperative period. Adequate oxygen delivery is optimised by maintaining good circulation rather than optimizing inspired oxygen concentration (SpO₂ per cent).⁴⁹ Therefore, focusing more attention on minimizing volume depletion and optimizing cardiac output during operative period is recommended.

Smoking cessation:

Smoking increases perioperative cardio-respiratory complications and adversely affects wound healing. It is recommended to cease smoking 6–8 weeks prior to elective surgery.⁵⁰

Manage existing cardiac/ Respiratory conditions

It is important to optimize the cardiac and respiratory disease control prior to non-cardiac surgeries. Patients with severe diseases may be referred to relevant speciality clinics. When interventions are required prior to NCS, discussions should be undertaken to consider postponing surgery.

Heart failure:

It is well established that poorly controlled cardiac failure during the peri-operative period increases overall mortality and adverse cardiac events after NCS.⁵¹ Brain Natriuretic Peptide (BNP) and pro-BNP demonstrated some prognostic value in optimizing heart failure therapy pre-operatively. It is recommend delaying elective procedures for three months in patients with severe decompensated heart failure to optimize control. It is advisable to continue BB and ACEI/ARB in such patients, peri-operatively.⁵² Heart failure with well controlled volume status is not associated with adverse cardiac outcomes peri-operatively.⁵³ The validity of echocardiogram in stable heart failure is uncertain and only useful in initial diagnosis and when change of the management is required.⁵⁴

Valvular heart disease:

It is recommended to have an echocardiogram if progressive symptoms are reported, or if one has not been performed within a year. It is also advisable to look for conduction defects in such patients where peri-valvular fibrosis could predispose to arrhythmias.⁵⁵

The AHA/ACC Valvular Heart Disease Guidelines recommends valvular intervention for patients with symptomatic severe valvular disease who meet the indications for intervention, prior to NCS.⁵⁷ Patients with congenital heart disease face a risk of higher mortality, thus perioperative anaesthetic management and planning is critical in those patients.^{56,57} Indications for antibiotic prophylaxis for valvular heart disease is well explained in the Australian Therapeutic Guidelines and is indicated only in certain non-cardiac procedures (Table 4).⁵⁸

Table 4 Procedures for which antibiotic prophylaxis indicated⁵⁸

Cardiac conditions for which endocarditis prophylaxis is recommended	Procedures	Details of the procedure
Prosthetic cardiac valve Prosthetic material used for cardiac valve repair, (annuloplasty rings and chords)	Dental procedures	<ul style="list-style-type: none"> Involving manipulation of the gingival or periapical tissue Perforation of the oral mucosa
	Dermatological or musculoskeletal procedures	<ul style="list-style-type: none"> Involving infected skin, skin structures or musculoskeletal tissues
Previous infective endocarditis	Respiratory tract or ear, nose and throat procedures	<ul style="list-style-type: none"> Tonsillectomy or adenoidectomy Invasive respiratory tract or ear, nose and throat procedures to treat an established infection
Congenital heart disease Rheumatic heart disease in high-risk patients	Genitourinary and gastrointestinal tract procedures	<ul style="list-style-type: none"> With an established infection

Acute Coronary Syndrome (ACS):

Pre-operative management of acute coronary syndrome is indicated in symptomatic patients. Guideline directed medical therapy is to be continued in such situations.⁸ This includes antiplatelets, BBs, statin therapy, risk factor modification and treating associated co-morbidities. However, coronary revascularization is indicated in symptomatic patients with optimal medical therapy and those who have high grade stenosis.⁵⁹

Prophylactic coronary revascularization prior to NCS fails to demonstrate beneficial effects in stable heart disease.⁶⁰ (see section under coronary revascularization)

Obstructive Sleep Apnoea (OSA):

OSA is very much under diagnosed and should be screened for in suspected patients in the pre-operative setting.⁶¹ OSA doubles the risk of post-operative cardiac and respiratory adverse events, prolonged hospital stay and consumes more hospital resources.⁶² OSA severity is assessed by the Apnoea-Hypopnea Index (AHI) measured during a sleep study. Moderate to high risk patients need respiratory or sleep physician review to assess suitability for Continuous Positive Airway Pressure (CPAP) therapy prior to NCS. The anaesthetists should be informed regarding such patients and precautions should be taken to minimize peri-operative complications.⁶³ People already on CPAP should bring their machine and use it during peri-operative period.

Deep Vein Thrombosis (DVT)/Pulmonary embolism (PE):

Patients with DVT and PE are usually on anticoagulants as part of their treatment. Other groups who are on anticoagulants are patients with atrial fibrillation for primary or secondary prevention of stroke and patients with mechanical valves. Continuation or withholding anticoagulation treatment during NCS depends on assessing the balance between bleeding risk of the procedure and thrombo-embolic risk. The type of anaesthesia is also affecting the anticoagulation plan during peri-operative period, however, the decision to bridge with heparin equivalent is an individualized decision.⁶⁴

Pulmonary artery hypertension (PAH):

PAH carries a very high risk of mortality and morbidity perioperatively.⁶⁵ A multidisciplinary approach with targeted therapy is useful to minimize adverse events during NCS.⁶⁶ Those patients with PAH should have their surgery in tertiary centres with advanced cardio-respiratory facilities.

Chronic Obstructive Airway Disease (COPD)/Asthma:

COPD is common in adults with a history of smoking and is usually associated with cardiovascular risk factors. Optimizing medical management of COPD/asthma and smoking cessation is indicated to improve peri-operative outcomes.⁶⁷ Pulmonary rehabilitation is indicated in severe disease when the NCS is compulsory.⁶⁸ Cardio-selective BBs are safe to continue during peri-operative period in patients with coronary disease.⁶⁹ Steroid treatments can be continued in acute exacerbations of asthma and COPD and guideline oriented therapy is indicated in such situations.⁷⁰ There is limited evidence to suggest better outcomes with peri-operative systemic steroid therapy in NCS.⁷¹

Cardiac implantable devices:

Patients could have various implantable devices including pacemakers, cardiac defibrillators, ventricular assisted devices, etc. All devices should be assessed prior to NCS and re-evaluated post-surgery. Electric current and magnetic interfaces during surgery could affect the performance of these devices.⁷²

Pacemakers are kept in asynchronous or triggered mode and implantable cardioverter-defibrillator (ICD) should be deactivated before starting diathermy or electro-cauterization. Devices are properly shielded when radiation or magnetic field is used. Most non-cardiac surgical procedures can be performed safely in patients with implanted cardiac devices.⁷³

Post-operative atrial fibrillation (POAF):

Patients undergoing NCS could have pre-existing AF, or POAF could develop during the peri-operative period. The incidence of POAF is higher during cardiac surgeries (20 to 40 per cent) and is about 3 per cent in NCS.⁷⁴ Multiple aetiologies, including surgical stress, predispose patients to POAF which increases the risk of perioperative cardioembolic strokes three-fold. Evidence for anticoagulant treatment in POAF is evolving and the current recommendation is to anti-coagulate where POAF is prolonged (>48hrs), and risk factors of stroke are present.⁷⁵

Other recommendations**Patient involvement in decision making:**

It is important to involve the patient in the discussion of perioperative planning.⁷⁶ In situations where the adverse event risk during and after surgery is very high, detailed discussions should be conducted regarding the decision of proceeding with the surgery versus conservative management.^{8,9}

Multidisciplinary approach:

In complex cardiac or respiratory conditions, multidisciplinary team involvement is recommended. Peri-operative physicians could get opinions from specialists such as cardiologists, respiratory physicians or thoracic surgeons depending on the associated condition.⁷⁷ It is also important to collaborate with the surgeon and the anaesthetist regarding relevant information. The intensive care team should be informed if high-level care is likely required after the procedure. Other healthcare professionals such as physiotherapy, occupational therapy or podiatry involvement may be necessary in relevant cases.⁷⁸

Supportive care:

Where the procedure could be futile, and a patient's cardiorespiratory co-morbidities are terminal and irreversible, early involvement of palliative care team may be recommended.⁷⁹ Physical and psycho-social support could be arranged through linking those patients to other available services and networks.⁷⁸

Post-operative care

Follow up and post-operative care after NCS is as important as pre-operative optimization. Pre-operative cardiorespiratory risk factors are an indication for close monitoring and review post-operatively. Common post-anaesthetic complications are managed in the recovery unit by the anaesthetist.⁸⁰

Intensive care requirement

Patients who require prolonged monitoring, inotropic and ventilator support are transferred to intensive care or high dependency units. Patients who will likely require such care are flagged pre-operatively. Triaging those patients who will benefit from intensive care unit (ICU) admission is elusive. It is important to utilize ICU resources in the post-operative period wisely and available guidelines and data in this area are limited.⁸¹

Early mobilization and multidisciplinary team approach

Post-surgical management pathways should be available for ward staff to optimize recovery of patients after NCS. Specific instructions relevant to the procedure should be included. Wound care, drain management, feeding, and bed mobility as examples.

Involvement of the multidisciplinary team including physiotherapists, occupational therapists, dieticians, social workers, and pharmacists is important to expedite post-surgical recovery.^{82,83}

Discharge planning**Rehabilitation and support**

Some patients with cardio-respiratory disease may require a period of rehabilitation after NCS. Early identification of such patients and referral to appropriate rehabilitation units should be completed with identified goals. Rehabilitation is known to improve outcomes in most patients after surgery.⁸⁴

Patients who can return home after NCS may require some support. For example, those who had orthopaedic surgeries with restricted weight bearing abilities will need physical assistance for several weeks. It is important to link those patients to supportive services through social workers.

Post-operative follow-up

All post-surgical patients require a documented follow-up plan. However, utilization of outpatient clinics after surgeries is sub-optimal.⁸⁵ Those who need physical follow up in the relevant surgical clinics should be given clear instructions. Discharge summaries should include this information, and a copy should be forwarded to patients' general practitioners.

Patients who require cardiology or respiratory reviews after hospital discharge are referred accordingly and operative complications and relevant investigations should be attached to the referrals. It is appropriate to review patients in a peri-operative clinic to ensure care is optimized post-surgically.

Conclusion

The risk stratification and management strategies for high and intermediate risk patients undergoing non-cardiac surgeries remains debatable.⁸⁶ The current major guidelines provide considerable insight into the management of such conditions.⁸⁻¹⁰ The above review is based on the available evidence in managing patients with cardio-respiratory diseases undergoing NCS. Further large-scale randomized studies are required to develop better pathways and guidelines to improve outcomes of high-risk patients journeying through NCS.

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