Invasive respiratory or vasopressor support and/or death as a proposed composite outcome measure for perioperative care research

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Authors' Contributions

Toshiyuki Mizota: This author conceptualized and designed the study, collected and analyzed the dataset, and drafted the manuscript.

Li Dong: This author helped design the study, analyzed and interpreted data, and critically revised and approved the manuscript.

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Abstract

Background: There is a need for a clinically relevant and feasible outcome measure to facilitate clinical studies in perioperative care medicine. This large-scale retrospective cohort study proposed a novel composite outcome measure comprising invasive respiratory or vasopressor support (IRVS) and death. We described the prevalence of IRVS in patients undergoing major abdominal surgery and assessed the validity of combining IRVS and death to form a composite outcome measure.

Methods: We retrospectively collected perioperative data for 2776 patients undergoing major abdominal surgery (liver, colorectal, gastric, pancreatic, or esophageal resection) at Kyoto University Hospital. We defined IRVS as requirement for mechanical ventilation for ≥24 hours postoperatively, postoperative reintubation, or postoperative vasopressor administration. We evaluated the prevalence of IRVS within 30 postoperative days and examined the association between IRVS and subsequent clinical outcomes. The primary outcome of interest was long-term survival. Multivariable Cox proportional regression analysis was performed to adjust for the baseline patient and operative characteristics. The secondary outcomes were length of hospital stay and hospital mortality.

Results: In total, 85 patients (3.1%) received IRVS within 30 postoperative days, 15 of whom died by day 30. Patients with IRVS had a lower long-term survival rate (1- and 3-year survival probabilities, 66.1% and 48.5% vs. 95.2% and 84.0%, respectively; $P < 0.001$, log-rank test) compared to those without IRVS. IRVS was significantly associated with lower long-term survival after adjustment for the baseline patient and operative characteristics (adjusted hazard ratio [HR], 2.72; 95% confidence interval [CI], 1.97–3.77; $P < 0.001$). IRVS was associated with a longer hospital stay (median [interquartile range], 65 [39–326] vs. 15 [12–24] days; adjusted $P < 0.001$) and a higher hospital mortality (24.7% vs. 0.5%; adjusted $P < 0.001$). Moreover, IRVS was adversely associated with subsequent clinical outcomes including lower long-term survival (adjusted HR, 1.78; 95% CI, 1.21–2.63; $P = 0.004$) when the analyses were restricted to 30-day survivors.

Conclusions: Patients with IRVS can suffer ongoing risk of serious morbidity and less long-term survival even if alive at postoperative day 30. Our findings support the validity of using IRVS and/or death as a composite outcome measure for clinical studies in perioperative care medicine.

Key Points Summary

Question: Is invasive respiratory or vasopressor support (IRVS) and/or death a clinically relevant outcome measure in perioperative care research?

Findings: Patients who received IRVS within 30 postoperative days had significantly worse outcomes compared to those who did not, even if they survived 30 postoperative days.

Meaning: Our findings support the validity of IRVS and/or death as a composite outcome measure in perioperative care research.

Worldwide, more than 200 million adults undergo major noncardiac surgery each year,[1] and reported short-term mortality rates after inpatient surgical procedures are between 0.4% and 4%.[2–4] Assuming a global perioperative mortality rate of 1%, more than two million patients undergoing surgery die during or immediately after surgery every year. These data suggest that improvements in perioperative care may lead to substantial public health benefit.

Often, 30-day mortality is regarded as the most important outcome measure in perioperative care research; however, it may not be the most relevant. It is recognized that 3%–18% of patients undergoing surgery have major complications,[2,4,5] possibly leading to loss of function and reduced long-term survival, even if they survive beyond 30 days postoperatively. Because most patients undergoing surgery anticipate long-term survival with a good quality of life, studies should be designed to test whether interventions can improve these outcomes. Although many outcome measures represent major postoperative complications (e.g., myocardial infarction,[6] stroke,[7] or pneumonia[8]), judging the presence or absence of these outcomes requires substantial time and efforts and often is impossible in retrospective studies. Therefore, a more feasible outcome

measure with minimal missing data would facilitate investigators to improve clinical study designs and promote perioperative care research.

Invasive respiratory or vasopressor support (IRVS), that is, intubation for respiratory failure or vasopressor use for hypotension, is used to define severe community-acquired pneumonia.[9–12] However, to our knowledge, it has never been used nor validated as an outcome measure in perioperative care settings. Because cardiac and pulmonary complications have significant impact on survival and length of stay after noncardiac surgery,[13–17] IRVS might serve as a useful marker of severe postoperative adverse events. In this study, we proposed a novel composite outcome measure, IRVS and/or death, for applications in clinical studies in perioperative care medicine. We described the prevalence of IRVS and, to assess the validity of combining IRVS and death to form a composite outcome measure, we examined the association between IRVS and subsequent clinical outcomes in patients undergoing major abdominal surgery. We hypothesized that patients who received IRVS within 30 postoperative days (PODs) would have a prolonged hospital course and lower long-term survival rate compared to those who did not, even if alive at POD 30.

Methods

Study Design, Setting, and Population

This single-center retrospective cohort study was conducted at Kyoto University Hospital, a teaching hospital with 1121 beds in Kyoto, Japan. The institutional review board approved the study protocol (approval number: R0672, July 26, 2016) and waived the requirement for informed consent. This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[18]

We recruited patients using the research database created for our previous study,[19] which investigated the relationship between intraoperative oliguria and acute kidney injury after major abdominal surgery. We included patients aged ≥18 years old who underwent major abdominal surgery under general anesthesia at Kyoto University Hospital from February 2010 to April 2015, from the introduction of the current electronic medical record system (PrimeGaia PRM-7400, Nihon Kohden, Tokyo, Japan) in the intensive care unit of our institution to the conception of this study. Major abdominal surgery included liver, colorectal, gastric, pancreatic, or esophageal resection by either laparotomy or a laparoscopic approach. For patients who underwent >1 surgery that met the inclusion

criteria during the study period, only the index case was included. Patients were excluded if they received mechanical ventilation via an endotracheal tube or tracheostomy or vasopressor (norepinephrine, epinephrine, vasopressin, ≥5 μg/kg/min dopamine, or ≥50 μg/min phenylephrine) within 30 days preoperatively. In addition, patients lost to follow-up within 30 PODs were excluded.

Data Collection

The research database for our previous study[19] included the data on age, sex, preoperative comorbidities, American Society of Anesthesiologists Physical Status (ASA-PS), type of surgery, postoperative hospital stay, and hospital mortality. In addition, the data on IRVS within 30 PODs and survival time were collected from the electronic medical record system. IRVS was defined as invasive respiratory and/or vasopressor support (definitions shown in Table 1). To define vasopressor support, we used the same criteria as those used to define hypoperfusion in a previous study.[20] Because 30-day mortality is a widely accepted outcome in perioperative care research,[21–24] we selected a time frame of 30 days to evaluate IRVS to assess the validity of combining IRVS within 30 PODs and 30-day

mortality. Survival time was measured from the date of surgery to death or last follow-up before January 11, 2018.

Statistical Analyses

The baseline patient characteristics and operative variables were compared by IRVS and survival status at POD 30. Categorical variables were compared using chi-square or Fisher's exact test, as appropriate, whereas continuous variables were compared using the Mann–Whitney *U* test. The primary outcome of interest was long-term survival. The secondary outcomes were length of hospital stay and hospital mortality. The Kaplan–Meier curve with the log-rank test was used to compare long-term survival between groups. Multivariable Cox proportional regression analysis was performed to assess the independent association of IRVS and long-term survival. In the multivariable model, the following factors were adjusted based on clinical relevance: age, sex, preoperative comorbidities (hypertension, diabetes mellitus, active congestive heart failure, and hemodialysis), type of surgery, and emergency status. Competing risk analyses were used to compare length of hospital stays. Medians and interquartile ranges of length of hospital

stays were obtained using the cumulative incidence estimates of discharge while alive accounting for death as a competing risk. The independent association of IRVS and length of hospital stay was assessed using the methods of Fine and Gray.[25] Multivariable logistic regression analysis was used to assess the independent association between IRVS and hospital mortality.

We expected that the association between IRVS and outcomes would vary depending on patient or operative characteristics. Accordingly, we assessed this potential heterogeneity by subgroup analyses. We compared long-term survival between 30-day survivors with and without IRVS in subgroups of age (≤65/>65 years), ASA-PS (I/II/III–IV), and type of surgery (colorectal/liver/gastric/others). We assessed the association between IRVS and long-term survival in each subgroup, followed by testing the interaction between the subgroups and IRVS.

We assessed the robustness of our findings using sensitivity analyses as follows: (1) restricting the assessment window for IRVS to seven PODs, (2) restricting the assessment window for IRVS to 14 PODs, (3) excluding patients with an ASA-PS of III–IV, and (4) excluding emergency surgery.

To assess whether patients with IRVS are worse off than those without IRVS even if alive at POD 30, we compared clinical outcomes between patients with and without IRVS after excluding those who died by POD 30.

Last, we performed multivariable logistic regression analysis to identify factors independently associated with the proposed composite outcome measure, IRVS and/or death within 30 PODs. Predicting patients who need intensive care from preoperative factors may aid in effective use of medical resources. The following variables were considered for entry to the model: age, sex, comorbidities (hypertension, diabetes mellitus, active congestive heart failure, and hemodialysis), type of surgery, and emergency status. A forward/backward stepwise variable selection minimizing the Akaike information criterion was used to determine the optimal combination of the predictors.

All the statistical tests were two-tailed, and $P < 0.05$ (a Dunnett corrected P value of <0.025 for comparisons of patients with IRVS and alive at or dead by POD 30 versus those without IRVS) was considered statistically significant. The statistical program R (available in the public domain at http://cran.r-project.org) was used to perform all the statistical analyses.

Results

Figure 1 presents a flow chart of the study population. In total, 2823 index major abdominal surgeries were identified in the study database spanning an approximately 5-year period from February 2010 to April 2015. After excluding four patients who received IRVS within 30 days preoperatively and 43 lost to follow-up within 30 PODs, 2776 patients (age, 20–90 years; 37.4% women) were included in this study.

The most common surgeries included colorectal (31.4%) and liver (29.3%) resection. Of the 753 patients (27.1%) admitted to the intensive care unit within 30 PODs, 696 had only scheduled admission postoperatively, whereas 57 were admitted emergently. Of the 2776 study patients, 85 (3.1%) received IRVS within 30 PODs; 51 (1.8%) received invasive respiratory support and 73 (2.6%) received vasopressor support. All the 15 patients (0.5%) who died by POD 30 received IRVS from surgery to death.

Table 2 shows patient characteristics and operative variables stratified by those with/without IRVS. The patients with IRVS had higher ASA-PS, were more likely to undergo emergency surgeries, were less likely to undergo laparoscopic surgeries, and had longer surgery duration and more blood loss.

The patients with IRVS had a significantly longer hospital stay and significantly higher hospital mortality compared to those without IRVS (Table 3). Survival analysis (median follow-up, 3.0 years; range, 0.0–7.9 years) demonstrated that the long-term survival rate was significantly less in the patients with IRVS compared to those without IRVS ($P <$ 0.001; log-rank test; Figure 2). The 1- and 3-year survival probabilities were 95.2% (95% confidence intervals [CI], 94.3%–95.9%) and 84.0% (95% CI, 82.4%–85.5%), respectively, for patients without IRVS, and 66.1% (95% CI, 54.8%–75.3%) and 48.5% (95% CI, 36.7%–59.3%), respectively, for those with IRVS. The patients who received IRVS had a median survival of 2.3 years (95% CI, 1.2–5.6 years). In contrast, median survival of those without IRVS could not be estimated because survival probability persisted at >70% even at the longest follow-up (7.9 years). Multivariable Cox proportional regression analysis revealed that IRVS was significantly associated with lower long-term survival after adjusting for the baseline patient and operative characteristics (adjusted hazard ratio [HR], 2.72; 95% CI, 1.97–3.77; $P <$ 0.0001; Supplemental Table 1).

In addition, we assessed the association between each component of IRVS and outcomes.

Both invasive respiratory support and vasopressor support were significantly associated with longer hospital stay, higher hospital mortality, and lower long-term survival rate (Supplemental Table 2 and Supplemental Figure 1).

Subgroup analyses based on age, ASA-PS, and type of surgery did not substantially affect point estimates for the association between IRVS and long-term survival. Although the adjusted HR varied across type of surgery, the point estimates for all the subgroups exceeded 1.0 (Figure 3). The relationships between IRVS and outcomes were qualitatively preserved across sensitivity analyses (Supplemental Tables 3, 4; Supplemental Figure 2). We found that 68.2% and 84.7% of the patients with IRVS first required IRVS within 7 and 14 PODs, respectively, and IRVS within 7 or 14 PODs was strongly associated with longer hospital stay, higher hospital mortality, and lower long-term survival (Supplemental Tables 3, 4; Supplemental Figure 2).

To assess whether patients with IRVS have poorer outcomes than those without even if they survive 30 PODs, we examined further the association between IRVS and outcomes after excluding those who died by POD 30. Among the 30-day survivors, the patients with IRVS had a significantly longer hospital stay (median [interquartile range], 56 [38–95]

vs. 15 [12–24] days; adjusted *P* <0.001; Supplemental Table 5), significantly higher hospital mortality (10.0% vs. 0.5%; adjusted *P* <0.001; Supplemental Table 5), and less long-term survival (adjusted HR, 1.78; 95% CI, 1.21–2.63; *P* = 0.004; Supplemental Figure 3, Supplemental Table 6) compared to those without IRVS.

Stepwise logistic regression analysis identified advanced age, male sex, type of surgery (liver, pancreatic, or esophageal resection), and emergency surgery as independent predisposing factors of the proposed composite outcome measure, IRVS and/or death within 30 PODs (Supplemental Table 7).

Discussion

We proposed a novel composite outcome measure, IRVS and/or death, for use in clinical studies in perioperative medicine. Of our patients undergoing major abdominal surgery, 3.1% received IRVS within 30 PODs, 17.6% of whom died by POD 30. As would be expected, IRVS was independently associated with a prolonged hospital course and lower long-term survival rate after adjusting for the baseline patient and operative characteristics. The associations between IRVS and subsequent clinical outcomes were qualitatively preserved across extensive subgroup and sensitivity analyses. Moreover, IRVS was adversely associated with subsequent clinical outcomes when the analyses were restricted to 30-day survivors. These data suggested that patients with IRVS will suffer ongoing risk of serious morbidity and less long-term survival even if alive at POD 30 and supported the validity of combining IRVS and death to form a composite outcome measure.

IRVS within 30 PODs combined with 30-day mortality has many advantages as an outcome measure in perioperative care research. First, IRVS and/or death is a more clinically relevant outcome than mortality alone. When we used 30-day mortality as an

outcome measure, patients who survived beyond 30 days postoperatively were considered to be a treatment success even if they developed severe complication and died soon after POD 30. In our dataset, 57.6% of patients who died without discharge from the hospital survived beyond 30 days postoperatively, and 36.8% of them required IRVS within 30 PODs. If 30-day survivors with major organ dysfunction requiring respiratory or vasopressor support occur more frequently in one group, this important difference will be missed when the focus is on mortality alone. In contrast, IRVS can capture these severely morbid patients who require intensive care.

Second, as is true for any major complication outcomes, combining IRVS and death can improve the statistical efficiency of studies compared to mortality alone. When IRVS was combined with death to form a composite outcome, the overall event rate in our dataset increased by approximately six times (from 0.5% for mortality alone to 3.1% for IRVS or mortality). This increase in event rate reduces the sample size required to show clinically important differences and increases the feasibility of clinical studies, especially when the treatment effect of interest affects components in the same direction. Moreover, by combining IRVS with death, we can avoid the problem of inflating the type I error rate

due to testing of multiple outcomes, and can eliminate the complexities involved with analyzing nonfatal outcomes for which death is a competing risk.

Third, data required to define IRVS usually are readily available and data missing are unlikely to occur compared to other outcome measures, such as myocardial infarction, stroke, or pneumonia. For example, postoperative myocardial infarction is determined by a combination of ischemic symptoms, electrocardiogram, cardiac biomarkers, echocardiography, and angiography.[6] Much time and effort are needed to collect these data, and such efforts usually suffer from a large amount of missing data, especially in retrospective studies.

Some studies of perioperative care use measures of healthcare resource use, such as intensive care unit admission or duration of critical care stay, as outcome measures.[26–29] Although these measures are important for health economics evaluations, they are not reliable surrogate markers of clinical outcome because they are affected by hospital and healthcare policy as well as by clinician behavior. In contrast, IRVS is likely to be a more objective marker of severity of illness compared to intensive care unit admission or duration of critical care stay across various institutions and health care systems.

The component variables of a composite outcome measures should not differ too widely in terms of severity. We demonstrated that, among the patients surviving at POD 30, both invasive respiratory support and vasopressor support were strongly associated with prolonged hospital course and lower long-term survival rate, and that the associations of invasive respiratory support and vasopressor support with outcomes do not substantially differ. These data supported the validity of combining invasive respiratory support, vasopressor support, and death to form a composite outcome measure. However, the interpretation of this composite outcome should be performed cautiously, particularly when the treatment effects of interventions or exposures differ across components.[30] For example, an intervention that reduces vasopressor support may reduce the composite of IRVS and death even during increased mortality. Therefore, it is vital to assess and report the heterogeneity of treatment effects across components.

We assessed IRVS within 30 days and 30-day mortality as binary outcomes, rather than calculating them as time-to-event outcomes. Although this approach is feasible to use and interpret, it might be more appropriate to use time-to-event analysis when: (1) time-to-event is important or (2) the dataset contains a certain amount of censoring. Although we

used a time-frame of 30 days to evaluate IRVS, most patients with IRVS first required respiratory or vasopressor support within 14 PODs, and in our sensitivity analyses, IRVS within 7 or 14 PODs also was strongly associated with a longer hospital stay and lower long-term survival rate. The optimal time-frame to evaluate IRVS remains to be determined.

Our study has many limitations that should be considered when interpreting these results. Assessments for IRVS are determined by the use of life support technologies, which are determined by clinicians; this may decrease the objectivity as an outcome measure. However, this limitation will be less important in the context of double-blind randomized clinical trials. Although we used long-term survival as the primary outcome, the survival probability at >3 years is not very reliable, particularly for those with IRVS because most events in this group occurred by 2–3 years, followed by a large gap with few events but a large proportion of censoring. Our single-center design might limit the generalizability of our results, and external validation is warranted to corroborate the current findings. In addition, our study included patients undergoing major abdominal surgery, so it is unclear whether our findings can be extrapolated to patients undergoing other surgeries. Further

research is required to evaluate the validity of IRVS as an outcome measure in various clinical settings.

In conclusion, IRVS during 30 PODs was associated with a prolonged hospital course and lower long-term survival rate in patients undergoing major abdominal surgery. Moreover, patients with IRVS had poorer outcomes even if they survived 30 PODs. Our findings supported the validity of IRVS combined with death as a composite outcome measure for clinical studies in perioperative care medicine. Further validation studies to assess the treatment effects of various interventions or exposures across mortality and components of IRVS are warranted.

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References

1. Weiser TG, Regenbogen SE, Thompson KD, et al. An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet.* 2008; 372: 139–44.

2. Gawande AA, Thomas EJ, Zinner MJ, Brennan TA. The incidence and nature of surgical adverse events in Colorado and Utah in 1992. *Surgery.* 1999; 126: 66–75.

3. Pearse RM, Moreno RP, Bauer P, et al. Mortality after surgery in Europe: a 7 day cohort study. *Lancet.* 2012; 380: 1059–65.

4. Khuri SF, Henderson WG, DePalma RG, Mosca C, Healey NA, Kumbhani DJ. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. *Ann Surg.* 2005; 242: 326–41.

5. Hall BL, Hamilton BH, Richards K, Bilimoria KY, Cohen ME, Ko CY. Does surgical quality improve in the American College of Surgeons National Surgical Quality Improvement Program: an evaluation of all participating hospitals. *Ann Surg.* 2009; 250: 363–76.

6. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Eur Heart J.* 2012; 33: 2551–67.

7. Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013; 44: 2064–89.

8. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control. 2008; 36: 309–32.

9. Buising KL, Thursky KA, Black JF, et al. A prospective comparison of severity scores for identifying patients with severe community acquired pneumonia: reconsidering what is meant by severe pneumonia. *Thorax.* 2006; 61: 419–24.

10. Chalmers JD, Singanayagam A, Hill AT. Systolic blood pressure is superior to other haemodynamic predictors of outcome in community acquired pneumonia. *Thorax.* 2008; 63: 698–702.

11. Charles PG, Wolfe R, Whitby M, et al. SMART-COP: a tool for predicting the need for intensive respiratory or vasopressor support in community-acquired pneumonia. *Clin Infect Dis.* 2008; 47: 375–84.

12. España PP, Capelastegui A, Gorordo I, et al. Development and validation of a clinical

prediction rule for severe community-acquired pneumonia. *Am J Respir Crit Care Med.* 2006; 174: 1249–56.

13. Lawrence VA, Hilsenbeck SG, Noveck H, Poses RM, Carson JL. Medical complications and outcomes after hip fracture repair. *Arch Intern Med.* 2002; 162: 2053–7.

14. Rosen AK, Geraci JM, Ash AS, McNiff KJ, Moskowitz MA. Postoperative adverse events of common surgical procedures in the Medicare population. *Med Care.* 1992; 30: 753–65.

15. Manku K, Bacchetti P, Leung JM. Prognostic significance of postoperative in-hospital complications in elderly patients. I. Long-term survival. *Anesth Analg.* 2003; 96: 583–9.

16. Greenstein AJ, Chassin MR, Wang J, et al. Association between minor and major surgical complications after carotid endarterectomy: results of the New York Carotid Artery Surgery study. *J Vasc Surg.* 2007; 46: 1138–44.

17. McFalls EO, Ward HB, Moritz TE, et al. Predictors and outcomes of a perioperative myocardial infarction following elective vascular surgery in patients with documented coronary artery disease: results of the CARP trial. *Eur Heart J.* 2008; 29: 394–401.

18. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Epidemiology.* 2007; 18: 805–35.

19. Mizota T, Yamamoto Y, Hamada M, Matsukawa S, Shimizu S, Kai S. Intraoperative oliguria predicts acute kidney injury after major abdominal surgery. *Br J Anaesth.* 2017; 119: 1127–34.

20. Heyland D, Muscedere J, Wischmeyer PE, et al. A randomized trial of glutamine and antioxidants in critically ill patients. N Engl J Med. 2013; 368: 1489–97.

21. Levin MA, Fischer GW, Lin HM, McCormick PJ, Krol M, Reich DL. Intraoperative arterial blood pressure lability is associated with improved 30 day survival. *Br J Anaesth.* 2015; 115: 716–26.

22. Lee SM, Takemoto S, Wallace AW. Association between withholding angiotensin receptor blockers in the early postoperative period and 30-day mortality: a cohort study of the veterans affairs healthcare system. *Anesthesiology.* 2015; 123: 288–306.

23. Monk TG, Bronsert MR, Henderson WG, et al. Association between intraoperative hypotension and hypertension and 30-day postoperative mortality in noncardiac surgery.

Anesthesiology. 2015; 123: 307–19.

24. Kim M, Brady JE, Li G. Interaction effects of acute kidney injury, acute respiratory failure, and sepsis on 30-Day postoperative mortality in patients undergoing high-risk intraabdominal general surgical procedures. *Anesth Analg.* 2015; 121: 1536–46.

25. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999; 94: 496–509.

26. Tritapepe L1, De Santis V, Vitale D, et al. Levosimendan pre-treatment improves outcomes in patients undergoing coronary artery bypass graft surgery. Br J Anaesth. 2009; 102: 198–204.

27. Peris A, Zagli G, Maccarrone N, et al. The use of Modified Early Warning Score may help anesthesists in postoperative level of care selection in emergency abdominal surgery. *Minerva Anestesiol.* 2012; 78: 1034–8.

28. Goepfert MS1, Richter HP, Zu Eulenburg C, et al. Individually optimized hemodynamic therapy reduces complications and length of stay in the intensive care unit: a prospective, randomized controlled trial. *Anesthesiology.* 2013; 119: 824–36.

29. Lee SH, Kim N, Lee CY, Ban MG, Oh YJ. Effects of dexmedetomidine on

oxygenation and lung mechanics in patients with moderate chronic obstructive pulmonary disease undergoing lung cancer surgery: A randomised double-blinded trial. *Eur J Anaesthesiol.* 2016; 33: 275–82.

30. Mascha, EJ, Sessler DI. Statistical grand rounds: design and analysis of studies with binary-event composite endpoints: guidelines for anesthesia research. *Anesth Analg.* 2011; 112: 1461–71.

Table 1. Definitions of invasive respiratory or vasopressor support

	Definitions
Invasive respiratory support	Mechanical ventilation through an endotracheal tube or tracheostomy >24 hours postoperatively (not including continuous positive airway pressure or noninvasive ventilation), or postoperative reintubation. Elective reintubation for reoperation was not considered as invasive respiratory support if the patient was extubated within 24 hours after reoperation.
Vasopressor support	Administration of vasopressor agents, such as norepinephrine, epinephrine, vasopressin, ≥5 μg/kg/min dopamine, or ≥50 μg/min phenylephrine, for >2 hours

Table 2. Patient characteristics and operative variables of patients with and without IRVS

	Without IRVS	With IRVS (*n* = 85)	
	(*n* = 2691)	Alive at POD 30 (*n* = 70)	Dead by POD 30 (*n* = 15)
Age (years)	66 (57–74)	70 (64–77)*	71 (63–72)
Male	1674 (62.2%)	52 (74.3%)	13 (86.7%)
Hypertension	857 (31.8%)	31 (44.3%)	6 (40.0%)
Diabetes mellitus	446 (16.6%)	20 (28.6%)*	3 (20.0%)
Active congestive heart failure	55 (2.0%)	1 (1.4%)	1 (6.7%)
Hemodialysis	19 (0.7%)	2 (2.9%)	0 (0.0%)

ASA-PS (1/2/3/4/missing)	697/1789/195/6/4	7/51/12/0/0*	0/11/4/0/0*
Type of surgery		*	
Colorectal	859 (31.9%)	11 (15.7%)	1 (6.7%)
Liver	778 (28.9%)	29 (41.4%)	7 (46.7%)
Gastric	518 (19.2%)	3 (4.3%)	1 (6.7%)
Pancreatic	377 (14.0%)	16 (22.9%)	4 (26.7%)
Esophageal	139 (5.2%)	9 (12.9%)	2 (13.3%)
Complex	20 (0.7%)	2 (2.9%)	0 (0.0%)
Laparoscopic surgery	1567 (58.2%)	14 (20.0%)*	3 (20.0%)*
Emergency surgery	34 (1.3%)	4 (5.7%)*	2 (13.3%)*

Duration of surgery (min)	345 (253–464)	587 (386–674)*	664 (481–738)*
Intraoperative blood loss	103 (20–424)	850 (230–1987)*	1800 (808–2950)*
Intraoperative red blood cell transfusion	221 (8.2%)	32 (45.7%)*	9 (60.0%)*
Intraoperative vasopressor infusion	279 (10.4%)	24 (34.3%)*	5 (33.3%)*

The data are presented as medians (interquartile range) or numbers (percentages). *$P < 0.025$ (significantly different with Dunnett correction), compared to patients without IRVS. IRVS, invasive respiratory or vasopressor support; POD, postoperative day; ASA-PS, the American Society of Anesthesiologists Physical Status.

Table 3. Association of IRVS with outcomes

	Without IRVS (*n* = 2690)	With IRVS (*n* = 85)	Adjusted association (95% CI)	*P* value
Length of hospital stay (days)	15 (12–24)	65 (39–326)	0.24 (0.19–0.29)*	<0.001
Hospital mortality	12 (0.5%)	21 (24.7%)	48.0 (21.4–108.0)	<0.001

One patient who was still hospitalized at the time of the data collection was excluded from the analyses, because length of hospital stay and hospital mortality in this patient could not be evaluated. Length of hospital stay was calculated using the cumulative incidence estimates of discharge while alive accounting for death as a competing risk. All the models were adjusted for age, sex, comorbidities (hypertension, diabetes mellitus, active congestive heart failure, and hemodialysis), type of surgery, and emergency status. Length of hospital stay was reported as HRs; hospital mortality as odds ratios. *HRs <1 denote longer hospital stay in patients with IRVS. IRVS, invasive respiratory or vasopressor support; CI, confidence interval; HR, hazard ratio.

Figure Legends

Figure 1. Flow chart of the study participants. IRVS, invasive respiratory or vasopressor support; POD, postoperative day.

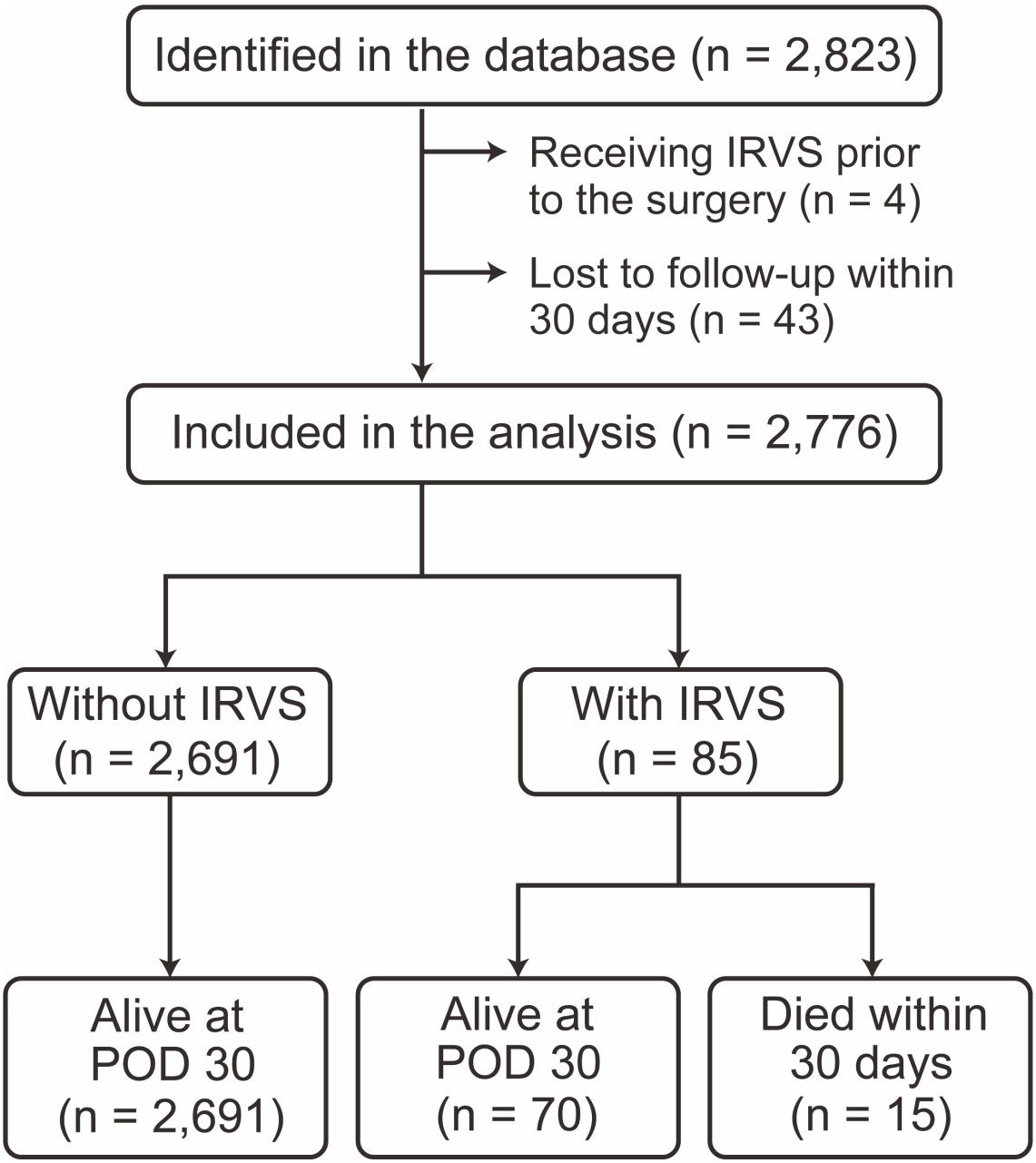


Figure 2. Kaplan–Meier curve comparing time to death of patients with and without IRVS. IRVS, invasive respiratory or vasopressor support.

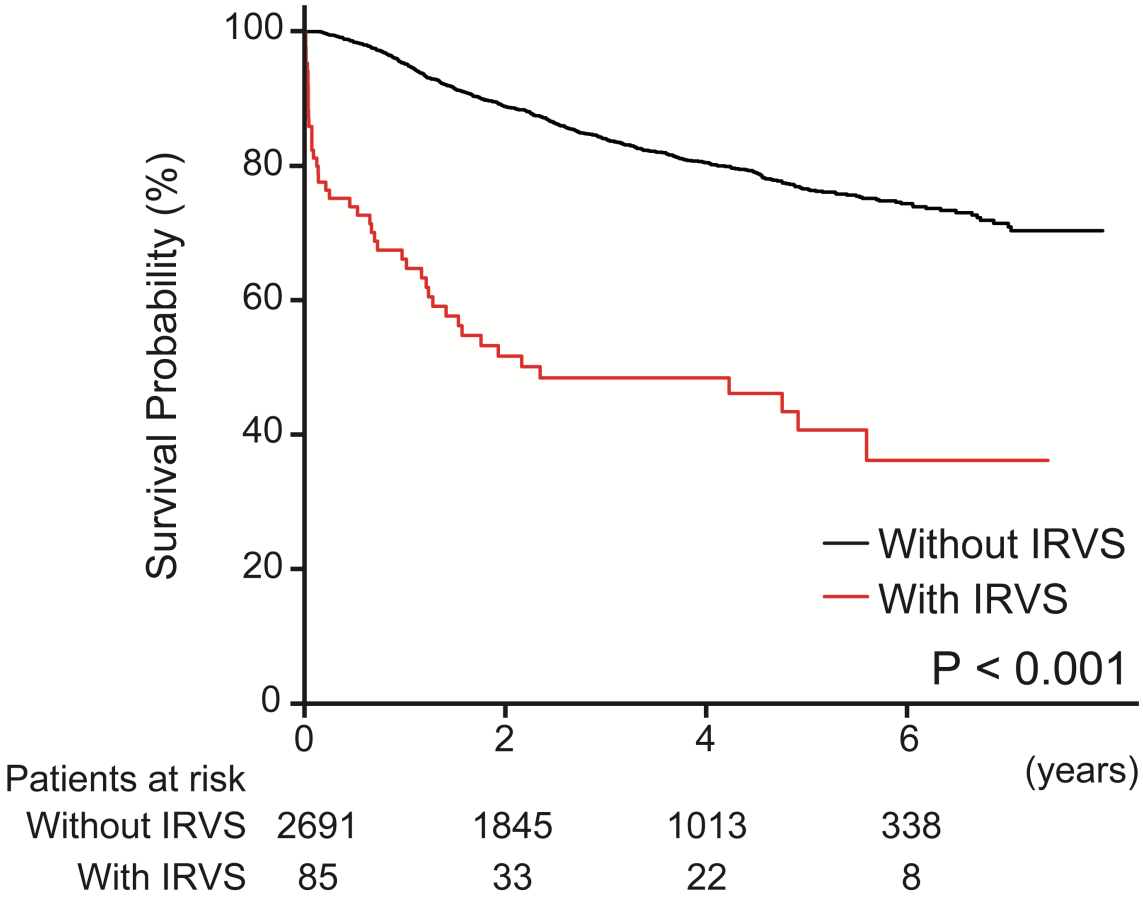
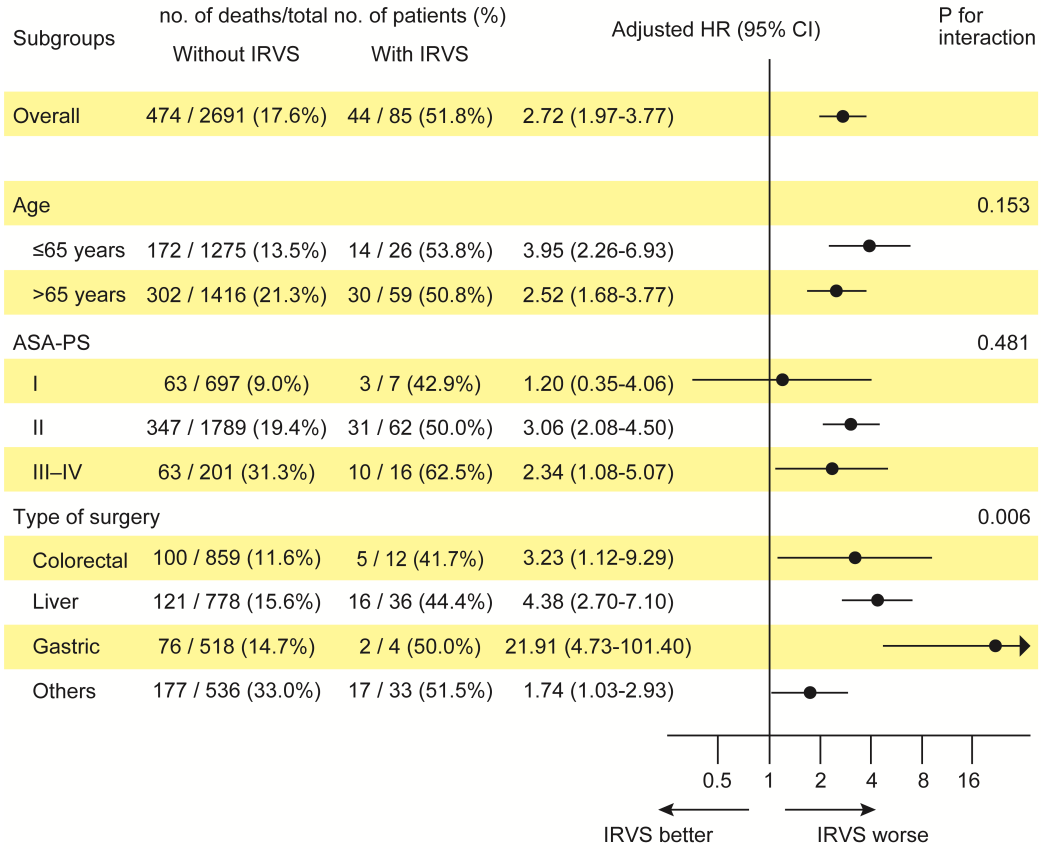


Figure 3. Subgroup analyses. The patients with missing ASA-PS are excluded from the subgroup analysis by ASA-PS. IRVS, invasive respiratory or vasopressor support; HR, hazard ratio; CI, confidence interval; ASA-PS, the American Society of Anesthesiologists Physical Status.



Supplemental Material

Supplemental Table 1. Multivariable Cox proportional regression analysis assessing independent association between IRVS and long-term survival

	Adjusted HR (95% CI)	*P* value
IRVS	2.72 (1.97–3.77)	<0.001
Age (per 1 yr)	1.03 (1.02–1.04)	<0.001
Male gender	1.19 (0.98–1.44)	0.080
Hypertension	1.16 (0.96–1.40)	0.129
Diabetes mellitus	1.25 (1.02–1.55)	0.036
Active congestive heart failure	1.88 (1.19–2.98)	0.007
Hemodialysis	1.00 (0.44–2.28)	0.993
Type of surgery		
Colorectal	1 (Reference)	
Liver	2.39 (1.84–3.11)	<0.001
Gastric	1.35 (1.01–1.82)	0.046
Pancreatic	4.01 (3.09–5.21)	<0.001
Esophageal	2.71 (1.88–3.91)	0.002
Complex	6.77 (3.60–12.71)	<0.001
Emergency surgery	1.95 (1.02–3.73)	0.044

IRVS, invasive respiratory or vasopressor support; HR, hazard ratio; CI, confidence interval.

Supplemental Table 2. Association of invasive respiratory support and/or vasopressor support with outcomes

	Without IRVS (n = 2,690)	Invasive respiratory support only (n =12)	Vasopressor support only (n = 34)	Both of invasive respiratory and vasopressor support (n = 39)
Length of hospital stay (days)	15 (12–24)	45 (30–78)	45 (36–65)	161 (72 to not estimable)
Hospital mortality	12 (0.45%)	2 (16.7%)	4 (11.8%)	15 (38.5%)

One patient who was still hospitalized at the time of the data collection was excluded from the analyses, because length of hospital stay and hospital mortality in this patient could not be evaluated. IRVS, invasive respiratory or vasopressor support.

Supplemental Table 3. Sensitivity analyses for length of hospital stay and hospital mortality

	Without IRVS	With IRVS	Adjusted association (95% CI)	*P* value
Restricting assessment window for IRVS to 7 PODs				
No. of patients	2717	58		
Length of hospital stay (days)	15 (12–24)	63 (38–234)	0.29 (0.22–0.37)*	<0.001
Hospital mortality	20 (0.74%)	13 (22.4%)	24.5 (10.6–56.9)	<0.001
Restricting assessment window for IRVS to 14 PODs				
No. of patients	2703	72		
Length of hospital stay (days)	15 (12–24)	64 (39 to not estimable)	0.24 (0.19–0.31)*	<0.001
Hospital mortality	14 (0.52%)	19 (26.4%)	49.5 (21.5–114.0)	<0.001
Excluding patients with an ASA-PS of III–IV				
No. of patients	2489	69		
Length of hospital stay (days)	15 (12–24)	65 (39 to not estimable)	0.22 (0.18–0.29)*	<0.001
Hospital mortality	11 (0.44%)	18 (26.1%)	52.3 (21.9–125.0)	<0.001
Excluding emergency surgery				
No. of patients	2656	79		

Length of hospital stay (days)	15 (12–24)	64 (38–282)	0.24 (0.19–0.30)*	<0.001
Hospital mortality	12 (0.45%)	18 (22.8%)	41.6 (18.2–95.0)	<0.001

One patient who was still hospitalized at the time of the data collection was excluded from the analyses, because length of hospital stay and hospital mortality in this patient could not be evaluated. Length of hospital stay was calculated using the cumulative incidence estimates of discharge while alive accounting for death as a competing risk. All the models were adjusted for age, sex, comorbidities (hypertension, diabetes mellitus, active congestive heart failure, and hemodialysis), type of surgery, and emergency status. Length of hospital stay was reported as HRs; hospital mortality as odds ratios. *HRs <1 denote longer hospital stay in patients with IRVS. IRVS, invasive respiratory or vasopressor support; CI, confidence interval; POD, postoperative day; ASA-PS, the American Society of Anesthesiologists Physical Status; HR, hazard ratio.

Supplemental Table 4. Sensitivity analyses for independent association between IRVS and long-term survival

	no. of deaths/total no. of patients (%)		Adjusted HR (95% CI)	*P* value
	Without IRVS	With IRVS		
Restricting assessment window for IRVS to 7 PODs	491/2718 (18.0%)	27/58 (46.6%)	1.93 (1.28–2.89)	0.002
Restricting assessment window for IRVS to 14 PODs	479/2704 (17.7%)	39/72 (54.2%)	2.67 (1.89–3.78)	<0.001
Excluding patients with an ASA-PS of III–IV	411/2490 (16.5%)	34/69 (49.3%)	2.83 (1.97–4.06)	<0.001
Excluding emergency surgery	468/2657 (17.6%)	40/79 (50.6%)	2.69 (1.93–3.77)	<0.001

All the models were adjusted for age, sex, comorbidities (hypertension, diabetes mellitus, active congestive heart failure, and hemodialysis), type of surgery, and emergency status. IRVS, invasive respiratory or vasopressor support; HR, hazard ratio; CI, confidence interval; POD, postoperative day; ASA-PS, the American Society of Anesthesiologists Physical Status.

Supplemental Table 5. Association of IRVS with outcomes in patients who were alive at POD 30

	Without IRVS (n = 2,690)	With IRVS and alive at POD 30 (n = 70)	Adjusted association (95% CI)	*P* value
Length of hospital stay (days)	15 (12–24)	56 (38–95)	0.32 (0.26–0.38)*	<0.001
Hospital mortality	12 (0.5%)	7 (10.0%)	14.8 (5.1–42.5)	<0.001

One patient who was still hospitalized at the time of the data collection was excluded from the analyses, because length of hospital stay and hospital mortality in this patient could not be evaluated. Length of hospital stay was calculated using the cumulative incidence estimates of discharge while alive accounting for death as a competing risk. All the models were adjusted for age, sex, comorbidities (hypertension, diabetes mellitus, active congestive heart failure, and hemodialysis), type of surgery, and emergency status. Length of hospital stay was reported as HRs; hospital mortality as odds ratios. *HRs <1 denote longer hospital stay in patients with IRVS. IRVS, invasive respiratory or vasopressor support; POD, postoperative day; CI, confidence interval; HR, hazard ratio.

Supplemental Table 6. Multivariable Cox proportional regression analysis assessing independent association between IRVS and long-term survival in patients who were alive at POD 30

	Adjusted HR (95% CI)	*P* value
IRVS	1.78 (1.21–2.63)	0.004
Age (per 1 yr)	1.03 (1.02–1.04)	<0.001
Male gender	1.17 (0.96–1.42)	0.113
Hypertension	1.17 (0.97–1.42)	0.101
Diabetes mellitus	1.27 (1.03–1.57)	0.028
Active congestive heart failure	1.75 (1.10–2.80)	0.019
Hemodialysis	1.19 (0.52–2.72)	0.681
Type of surgery		
Colorectal	1 (Reference)	
Liver	2.37 (1.82–3.08)	<0.001
Gastric	1.33 (0.99–1.80)	0.060
Pancreatic	4.06 (3.12–5.28)	<0.001
Esophageal	2.76 (1.91–4.01)	<0.001
Complex	7.43 (3.96–13.93)	<0.001
Emergency surgery	1.79 (0.87–3.67)	0.112

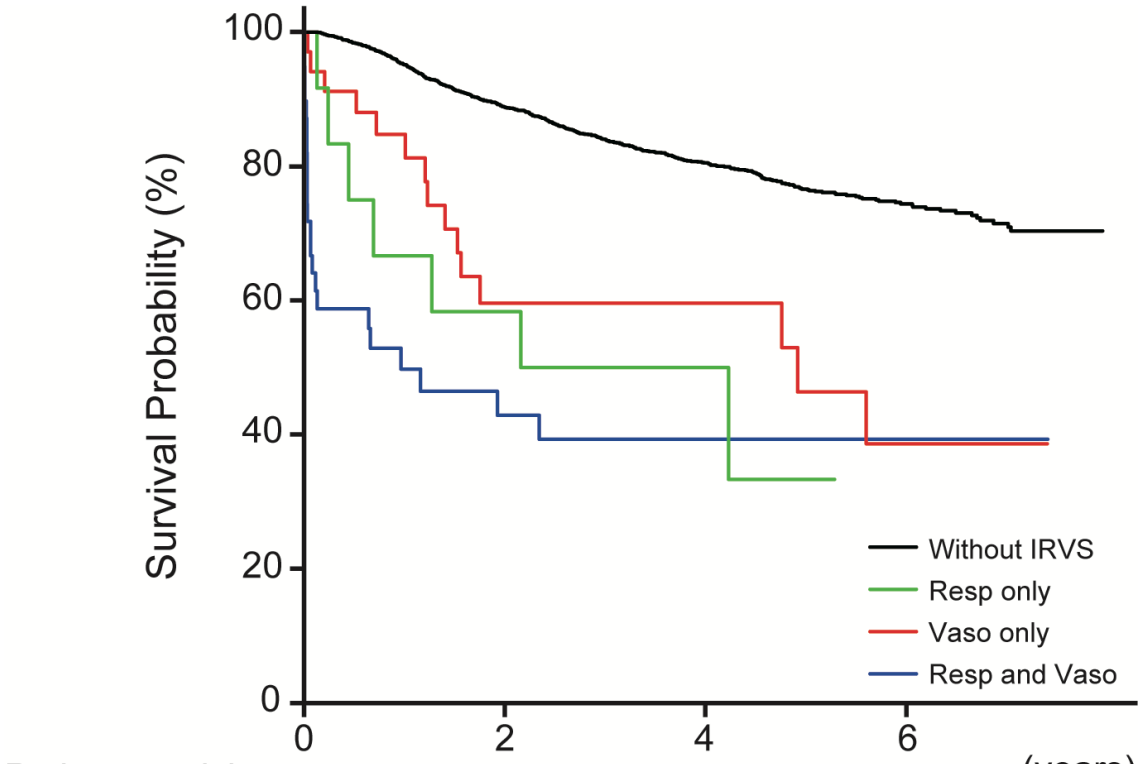
IRVS, invasive respiratory or vasopressor support; POD, postoperative day; HR, hazard ratio; CI, confidence interval.

Supplemental Table 7. Multivariable logistic regression analysis of independent predisposing factors for the composite of IRVS and death

	Adjusted odds ratio (95% CI)	*P* value
Age (per 1 yr)	1.05 (1.03–1.07)	<0.001
Male sex	1.82 (1.08–3.06)	0.025
Type of surgery		
Colorectal	1 (Reference)	
Liver	4.95 (2.48–9.88)	<0.001
Gastric	0.62 (0.20–1.97)	0.420
Pancreatic	4.89 (2.31–10.40)	<0.001
Esophageal	6.86 (2.87–16.40)	<0.001
Complex	5.57 (1.02–30.40)	0.047
Emergency surgery	10.00 (3.71–27.20)	<0.001

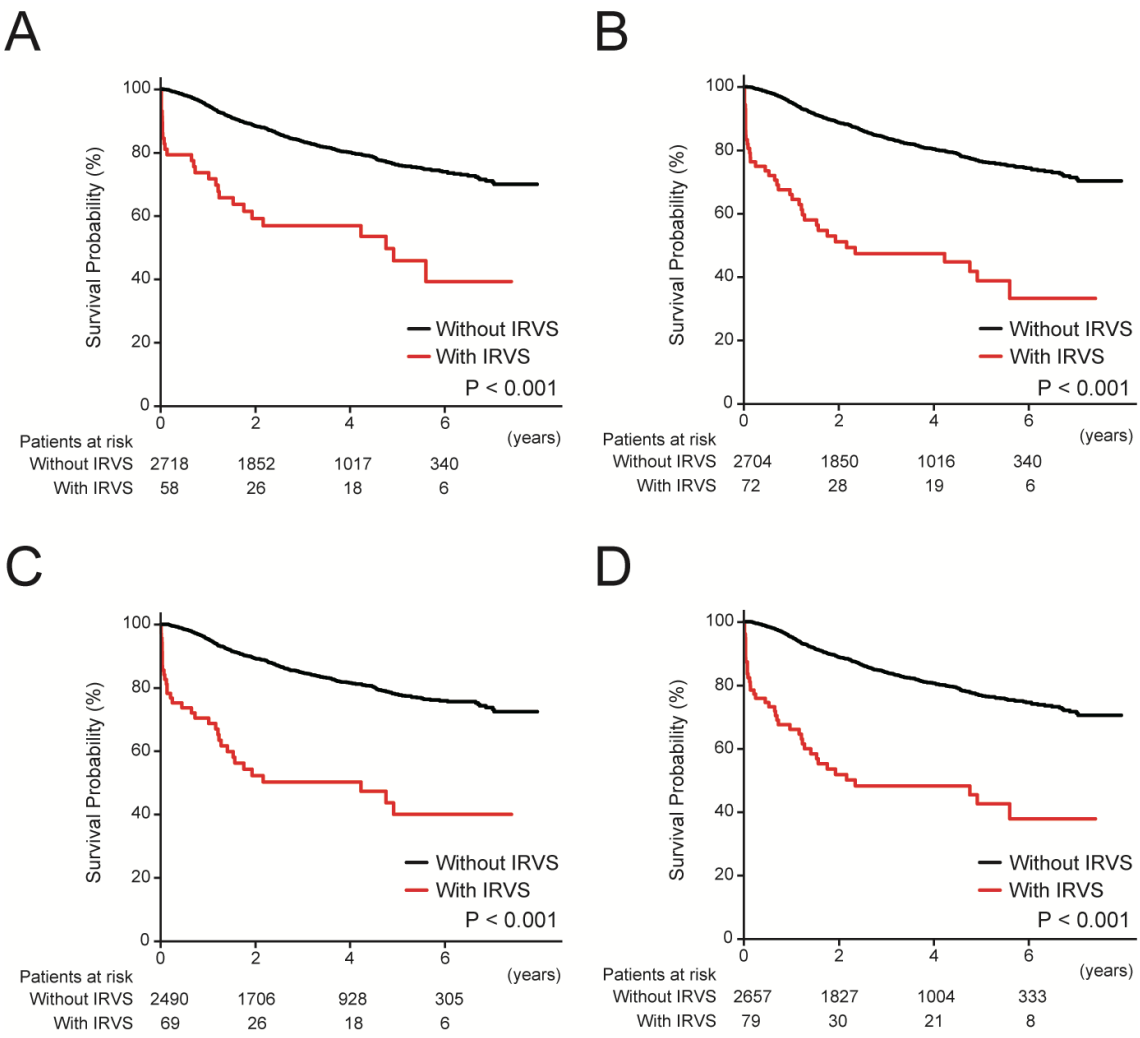
IRVS, invasive respiratory or vasopressor support; CI, confidence interval.

Supplemental Figure 1. Association of invasive respiratory support and/or vasopressor support with long-term survival. IRVS, invasive respiratory or vasopressor support; Resp, invasive respiratory support; Vaso, vasopressor support.



Patients at risk				
Without IRVS	2691	1845	1013	338
Resp only	12	7	3	0
Vaso only	34	14	11	5
Resp and Vaso	39	12	8	3

Supplemental Figure 2. Sensitivity analyses for long-term survival. A: Restricting the assessment window for IRVS to seven PODs; B: Restricting the assessment window for IRVS to 14 PODs; C: Excluding patients with an ASA-PS of III–IV; D: Excluding emergency surgery. IRVS, invasive respiratory or vasopressor support; POD, postoperative day; ASA-PS, the American Society of Anesthesiologists Physical Status.



Supplemental Figure 3. Kaplan–Meier curve comparing time to death of patients with and without IRVS who were alive at POD 30. IRVS, invasive respiratory or vasopressor support; POD, postoperative day.