# Attributable mortality of ventilator-associated pneumonia: replicating findings, revisiting methods

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Online data supplement

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**Detailed list of variables and definitions**

*Main time-varying exposures and primary outcomes*

Mechanical ventilation

A patient's daily mechanical ventilation (MV) status was derived from patient-specific MV episodes. Daily MV status was coded 1 if the MV episode covered the corresponding calendar date, and 0 otherwise. An MV episode was defined as an uninterrupted time window in which at least 2 ventilation parameters (including but not restricted to PEEP, tidal volume, $FiO_2$, $SpO_2$, respiratory rate, I:E ratio, pressure support, mean airway pressure) were registered. A time window is considered uninterrupted if there were no gaps of more than 24 hours with less than 2 registered ventilation parameters. Ventilation parameters (set and measured values) were either routinely entered by nursing staff every 30 minutes to 2 hours (depending on the parameter) or automatically registered through a connected monitoring device (such as respiratory rate and $SpO_2$) and validated by nursing staff every 30 minutes. Internal code was used to calculate MV episodes from time-dependent ventilator parameters.

Ventilator-associated pneumonia (VAP)

Hospital-acquired pneumonia diagnosed in patients under mechanical ventilation for 48 hours or longer, or in patients who had been extubated for less than 48 hours after mechanical ventilation for at least 2 days (1). Following (2), we included only pneumonia with high and moderate probability. Pneumonia was considered to be highly probable in the case of presence of a new or worsening infiltrate on chest X-ray, together with clinical signs of sepsis and new respiratory symptoms (increased sputum, increased purulence of sputum, worsening oxygenation), and a semi-quantitative score of 1+ growth or more of a pathogen in a good-

quality respiratory sample. Pneumonia was considered to be moderately probable in the case of all previous criteria but in the absence of respiratory pathogens or growth below the threshold of 1+. This is a clinically pragmatic definition that closely matches reality and has high concordance with the CDC definition (2).

Suspected VAP diagnosis was entered by the treating intensive care physician in the Computer-based Surveillance and Alerting of nosocomial infections, Antimicrobial Resistance and Antibiotic consumption in the ICU (COSARA) system.

Two hundred ninety-five (295) patients were registered with suspected VAP. Forty (40) of these were not microbiologically confirmed and had low probability on clinical re-evaluation after 48-72h of empirical antibiotic therapy. Of the remaining 255, 44 patients were coded with a VAP diagnosis within 48 hours after ICU admission and within 48 hours after the start of the first episode of mechanical ventilation (as defined above). Assuming correct ICU admission times, correct coding/registration of mechanical ventilation episodes at the ICU, we considered these patients as either misdiagnosed by the treating physician (because failure to adhere to the aforementioned definition of VAP) or as correctly diagnosed, but not ICU-acquired (possibly due to mechanical ventilation prior to ICU admission). These 'ambiguous' VAP cases were recoded as non-VAP, and remaining VAP cases were considered as 'incident VAP cases', i.e. ICU-acquired VAP due to mechanical ventilation administered at the ICU. One of the remaining 211 VAP cases was excluded from the final analysis due to a missing APACHE II score (cf. flow diagram in Figure 1 in the main manuscript).

VAP diagnosis may have been susceptible to differential misclassification bias in patients with treatment limitation decisions (cf. below), i.e. VAP cases could have been missed relatively more often (false negatives) in patients with DNR codes because accurate diagnosis may not have been as pressing for considering adequate therapy options as for patients without a DNR code. However, in estimating the population-attributable fraction (using approach 4), we aimed

to correct for such potential detection bias by adjusting for time-varying DNR code as a potential confounder in the Cox proportional hazards model to calculate inverse probability weights (see section 'Cox proportional hazards model for the daily probability of acquiring VAP'). There is, however, no guarantee that this may have completely eliminated potential detection bias.

Daily VAP acquisition status was coded 1 from the first calendar date of VAP diagnosis and 0 otherwise. Following (3), we coded daily VAP status as 'having acquired VAP on the current calendar date or earlier' (i.e. VAP status was coded 1 even if clinical cure from VAP had occurred). Clinical cure after VAP acquisition was considered irrelevant as we aimed to estimate attributable ICU mortality due to VAP *acquisition* rather than that of time-varying VAP.

ICU death/discharge status and time

Time of death at the ICU and discharge from the ICU were entered by nursing staff in the Intensive Care Information System (ICIS), along with event status (ICU death/discharge). No information bias was expected because these involved hard endpoints. Nonetheless, one patient had a missing event status and was therefore discarded from the analysis, under the assumption of missing completely at random (MCAR) (see flow diagram; Figure 1 in the main text).

*Baseline covariates*

Admission category

Admission category was extracted from the ICIS and indicated whether a patient was admitted at the Medical ICU (MICU) or Surgical ICU (SICU), and whether admission to the SICU was considered for emergency or scheduled surgery.

Demographic data

Gender and date of birth was extracted from the ICIS, which retrieves this information through the Admission Discharge Transfer (ADT) feed at ICU admission. Age at ICU admission was derived from ICU admission date, which was entered manually at ICU admission, and the patient's date of birth. In addition, weight (kg) was either measured and retrieved from external hospital records, estimated by nursing staff or reported by the patient or their relatives, and entered in the ICIS by nursing staff. For 9 patients, weight was missing.

Charlson comorbidity index (updated)

The updated Charlson comorbidity index was calculated from patient admission data in the ICIS using weights as described in (4), using internal code (mapping and code available upon request). Data on rheumatologic disease was missing for all patients. The corresponding weight of 1 was therefore replaced by 0. The same principle was applied whenever information on other conditions was missing for certain patients.

Acute Physiology and Chronic Health Evaluation (APACHE) II score

APACHE II score (5) was calculated using proprietary code of GE Centricity Critical Care 8.1 and incorporated in the ICIS. Eight cases with missing APACHE score were deleted and a

complete case analysis was performed under the assumption of missing completely at random (MCAR) (see flow diagram; Figure 1 in the main text).

*Time-varying covariates*

Antibiotic therapy

Daily binary indicators of antibiotic (AB) therapy (1 if AB received; or 0 otherwise) were derived from time windows in which a specific AB was administered, as entered by physicians in the COSARA database. A detailed list of included AB can be found in (6).

Vasoactive agent use

Daily binary indicators of vasoactive agent (VA) use (1 if VA received; or 0 otherwise) were derived from registered infusion rates of vasoactive agents (including dobutamine, dopamine, epinephrine, milrinone, norepinephrine and vasopressin) in the ICIS database.

Enteral feeding

Daily binary indicators of enteral feeding (EF) were derived from registered doses in the ICIS database.

Corticosteroids

Daily binary indicators of administration of corticosteroids (1 if total day-specific dose >0.5 mg/kg; or 0 otherwise) were derived from estimated/measured weight at admission (cf supra) and corticosteroid doses as entered by nursing staff (in case of oral administration or intravenous (IV) injection) or registered through IV infusion pumps in the ICIS (aggregated per patient per day). For 2 patients who received corticosteroids, weight was missing, such that

dose/kg could not be calculated. Each of these patients had only one recorded dose. Based on other non-missing demographic characteristics (gender and age), it was assumed that these doses exceeded 0.5mg/kg (i.e. under the assumption that the weight of these patients did not exceed the maximum weight at which the respective doses >0.5mg/kg).

Hemodialysis

Timestamps on hemodialysis episodes were missing from the ICIS and COSARA databases. This information was therefore derived from recorded ultrafiltration rates. Daily binary indicators of the presence of ultrafiltration rate records (1 if present; 0 otherwise) were calculated from the ICIS database.

Tracheotomy tube

Daily binary indicators of the presence of a tracheotomy tube (1 if present; 0 otherwise) were derived from time windows from placement to removal of tracheotomy tube, as entered by nursing staff in the ICIS database. In case no timestamp for removal of tracheotomy tube was registered, tracheotomy tube was assumed to be present until ICU death or discharge.

Treatment limitation decisions (TLDs)

Daily TLD codes (code 0-4) were derived from registered do-not-resuscitate (DNR) codes, as entered by physicians in the ICIS database, and their timestamps. In case a DNR code was changed on a particular day, only the last registered DNR code by the end of that day was with withheld as the day-specific DNR code. The last registered DNR code of a patient was assumed to hold until time of ICU death or discharge. The following progressive coding scheme was used (also see (7)):

- Code 0 = full therapy (no therapy restrictions);

- Code 1 = no cardiopulmonary resuscitation, no defibrillation;
- Code 2 = withholding of therapy (therapy restrictions that may include no referral to the ICU, no dialysis, no upgrading of antibiotics, no vasopressors or inotropes, no colloids or cristalloids in case of hypotension, no intubation and mechanical ventilation, no blood transfusions or blood cultures, no metabolic correction, no surgical procedures);
- Code 3 = withdrawal of life-sustaining therapy (only comfort care; may include pain relief and symptom control, discontinuation of vasopressors/inotropes, discontinuation of mechanical ventilation);
- Code 4 = withdrawal of all active and supportive therapy, mechanical ventilation

Due to data sparsity codes 2, 3 and 4 were collapsed into one category.

Other hospital-acquired infections

Daily binary indicators of suspected or confirmed bacterial and fungal infections (1 if suspected or confirmed; 0 otherwise) were derived from infection diagnosis as entered in the COSARA database by treating physicians. More specifically, separate daily indicators were calculated for

- bacterial abdominal infections
- bacterial catheter-related infections
- bacterial respiratory infections
- bacterial urinary tract infections
- all other bacterial infections (including endocarditis, meningitis, encephalitis, neutropenic sepsis, other neurological infections, skin infection)
- fungal infections (including yeast infections and other fungal infections)

Sequential Organ Failure Assessment (SOFA) score

Daily SOFA scores (8) were extracted from the COSARA database. These were calculated as the sum of six SOFA subscores, each of which are scored from 0 to 4 and are calculated in real-time in the ICIS for each 24h interval from 5am of the current calendar day to 5am the next calendar day, based on available lab results imported in the ICIS, physiological parameters and administered drugs and interventions (as detailed in (9)). The six SOFA subscores reflect

- coagulation function
- renal function
- cardiovascular system function
- central nervous system function
- hepatic system function
- respiratory function

Higher scores reflect increasing levels of organ dysfunction. However, this score may in part reflect the subjective appraisal of a patient's condition by intensive care physicians because when a patient is not suspected to have a particular organ dysfuntion no tests are ordered beyond routine test and measurement procedures. Corresponding subscores that therefore may be missing are scored 0.

*Standard of care VAP prevention*

The following measures to prevent VAP are applied in our ICU: 1) use of short acting sedatives and analgetics and thrice daily assessment of sedation goals (morning, noon and evening rounds) 2) application of early mobilization and twice daily assessment of weaning readiness (morning and noon rounds) 3) use of oral chlorhexidine 4) 30% semi-recumbent positioning. Continuous subglottic aspiration is not systematically used.

**Comparison of statistical approaches with respect to emulation of a randomized controlled prevention trial**

The (time-dependent) population-attributable fraction (PAF) of ICU mortality due to VAP expresses the percentage of preventable cases in the ICU in the absence of VAP as a function of time since ICU admission. Under certain assumptions[1], its estimate can be interpreted as the relative mortality reduction that would be found in the ICU in a hypothetical RCT in which eligible patients are randomly assigned to receive either a fully effective bundle of preventive measures or standard of care (see 'Detailed list of variables and definitions').

Due to randomization, the cumulative incidence in the latter arm of this target prevention trial is expected to correspond to the observed cumulative incidence in an observational study (where all patients receive standard of care). This quantity can directly be estimated from a competing risk analysis (treating ICU discharge as a competing event for ICU death).

The cumulative incidence in the preventive bundle arm, on the other hand, corresponds to the 'counterfactual' VAP-free cumulative incidence. This quantity cannot readily be estimated from observational data. However, explicit description of the hypothetical target trial provides

[1]The sufficient set of assumptions entails consistency, no unmeasured confounding, positivity and no misspecification of the nuisance models (e.g. to estimate IP weights). A key component of consistency is that of 'well-defined interventions'. In particular, in our study, we aim to compare outcomes under 'standard-of-care' and 'a fully effective bundle of VAP prevention'. The latter intervention may not be sufficiently well-defined because, as of yet, such a bundle is unavailable. Note that this inherent vagueness may hinder an unambiguous interpretation of the PAF estimates in our study, because the definition in itself determines how 'counterfactual' interventions may be linked to the data (another key component of consistency) and may guide expert opinion on sufficient adjustment sets that suffice for confounding control. For instance, due to the inherent vagueness of the prevention bundle, we may have adjusted away preventive effects via manipulable confounders that may be effective targets for VAP prevention. For more details on this discussion, see (22,23).

a roadmap for statistical analysis (10,11) and offers a general framework for comparing existing analytical approaches. In particular, estimation of the 'counterfactual' VAP-free cumulative incidence poses additional challenges as it necessarily relies on causal assumptions that cannot be verified from the data at hand. Although proposed estimation approaches for 'emulating' this hypothetical trial arm (or counterfactual scenario) differ in the extent to which such causal assumptions are made explicit, each approach involves some form of up-weighting VAP-free events from observational data.

The (often implicit) rationale behind weighting events is as follows. As patients acquire VAP, they are no longer compatible with receiving a fully effective preventive bundle in the target prevention trial (or with the counterfactual scenario) we aim to emulate. As their subsequent events are therefore discarded from further statistical analysis, they should transfer their weight to patients who have remained VAP-free, thereby accounting for the selection of the latter group of 'compatible' patients. By receiving additional weight in the analysis, VAP-free patients substitute for VAP-infected patients being excluded from the original population for which we aim to estimate the hypothetical CI had no one acquired VAP. As illustrated in more technical detail in (12), it turns out that all proposed methods under comparison apportion weights to VAP-free events that are inversely proportional to the overall amount of selection, so as to 'reconstruct' the original patient population. However, their respective weighting schemes differ largely in terms of how well they respect the temporal ordering of events and how well they take into account the (possibly) selective nature of 'compatible' patients over time. Consequently, proposed approaches are successful at tackling different sources of bias to varying degrees. Successful emulation of the cumulative incidence in this hypothetical trial arm critically hinges on the following guiding principles.

First, the total amount of transferred weight at any given time wave should be inversely proportional to the likelihood of being VAP-free (i.e. degree of selection of VAP-free patients)

*until (at least) that time wave*. Deviations from this principle produce immortal time bias, because they fail to respect the temporal ordering of events. Such bias typically occurs when the analysis is restricted to never infected patients (i.e. patients who remained without VAP until the end of study follow-up) as in approach 1 (though not approaches 2—4). Indeed, such analysis implicitly weighs VAP-free events at each time wave according to the likelihood of remaining VAP-free until the end of study follow-up, which is only known at the ultimate VAP onset in the sample population.

Second, at any given time wave, weight transferred from newly VAP-infected patients should only be distributed among VAP-free patients that are *still hospitalized* at the ICU at that time wave. Deviations from this principle likewise fail to fully respect the timing of events. They often yield a more subtle form of time-dependent bias, which has only been documented recently (12,13). One widely advocated multi state modelling approach for estimating the PAF (14) (approach 2, along with approach 1, though not approaches 3—4) violates this second principle because it (implicitly) distributes the (correct) total amount of transferred weight at a given time wave evenly among all patients who did not acquire VAP by that time, including patients that already experienced a VAP-free event (i.e. patients that have died or been discharged by that time without VAP). This implies that a deceased VAP-free patient is not only weighed in the analysis at her time of death, to compensate for the depletion of VAP-infected patients by that time wave, but gets re-weighted after her death to compensate for further depletion of VAP-infected patients in the future.

Third, at any given time wave, VAP-infected patients should transfer weight to VAP-free patients with the same patient profile in terms of admission characteristics and evolution of disease severity up to that time wave. This is required to ensure comparability of patients in each of the arms of our target prevention trial, or in other words, to emulate randomized assignment of eligible patients to the preventive bundle arm. For instance, susceptible patients

who acquire VAP generally tend to be more severely ill than those who do not acquire VAP. Accordingly, the weight received by a VAP-free ICU patient who is severely ill at a particular time wave should be proportional to the degree of depletion of comparable VAP-infected patients with the same severity of illness up to that time. Deviations from this principle fail to account for the selective nature of VAP-free ICU patient profiles over time and may result in estimates of the counterfactual VAP-free cumulative incidence that are systematically biased downward. Approach 3 (15–18), which has rarely been applied for estimation of time-dependent PAFs , violates this third principle (along with approaches 1 and 2). This is because, in their current form, multi state modelling approaches only allow to accommodate the selective nature of VAP-free patients insofar as this is captured by admission characteristics, but not to the extent that this is driven by time-dependent confounding factors that evolve since admission. This is a less well understood but important shortcoming because, for instance, prior to acquiring VAP, patients may deteriorate further and may therefore be at increased risk of VAP, even if, at ICU admission, their prognosis is similar to that of patients who eventually do not acquire VAP. Consequently, adjustment for time-dependent confounding (or equivalently, adjustment for the ensuing differential selection of VAP-free patients / informative censoring of VAP-infected patients) should not only be made at baseline, e.g. for severity of illness indicators recorded at time of admission, but also for the evolution of such indicators over time. Generalized methods, abbreviated g-methods (19,20), comprise a class of methods, some of which, in particular inverse probability (IP) weighting (approach 4), can be characterized as a natural generalization of approach 3 that enables additionally respecting this third principle by tackling issues related to the time-dependent nature of confounding and selection of VAP-free patients (12). In contrast to the first two principles, one's ability to correctly adhere to this third principle necessarily relies on subject matter knowledge of the selective nature of VAP-free

patients, especially in relation with the patient outcome under study, i.e. ICU mortality, and the availability of data on relevant characteristics that sufficiently capture this selective nature.

**Cox proportional hazards model for the daily probability of acquiring VAP**

*Causal assumptions encoded in a causal diagram*

Figure E1 (*A*) displays a simplified causal diagram that depicts the time-dependent setting (restricted to VAP acquisition at time waves *t*-1 and *t*) along with the causal assumptions with respect to measured baseline and time-varying covariates. Specifically, the red nodes capture a set of covariates, as listed below (heading 'Adjustment set and simplifying model and causal assumptions'), that were deemed sufficient to adjust for confounding (i.e. assumption of no unmeasured confounding). The temporal ordering of the variables is explicitly displayed in the causal diagram by representing earlier measurements and events to the left and later measurements and events to the right. Pink pathways indicate biasing pathways of the effect of time-dependent VAP on ICU mortality.

*Rationale behind inverse probability weighting*

Inverse probability (IP) weighting aims to resolve this confounding bias by constructing a pseudo-population that consists of the original study population under the hypothetical scenario that all patients had remained without VAP until the end of hospitalization (i.e. until ICU death or discharge). It does so in a way that aims to render VAP acquisition at time *t* among hospitalized patients that have remained without VAP up until time *t*-1 independent of the measured covariate history up until time *t*-1 or, in other words, in a way that aims to restore covariate balance (up until time *t*-1) between incident VAP cases and VAP-free patients at time *t* among hospitalized patients that have remained without VAP up until time *t*-1. In graphical terms, IP weighting removes all incoming edges into time-varying VAP such that biasing pathways are resolved, as displayed in the modified causal diagram in Figure E1 (*B*).

*Adjustment set and simplifying model and causal assumptions*

In order to calculate IP weights, a time-dependent Cox proportional hazards model was fitted for time-to-VAP (or, equivalently, the daily probability of acquiring VAP) in function of the available covariate history, including admission characteristics and time-dependent factors, as detailed below.

At each time wave, the history of daily measures of interventions and treatments was summarized in terms of their presence or absence on the day before possible VAP acquisition and by the total number of previous days exposed to each of these interventions and treatments. It was assumed that this summary coding of the covariate history was sufficient for confounding adjustment. To acknowledge that SOFA scores and antibiotic treatment the day before possible VAP diagnosis may be surrogate markers for an incubating infection, and hence potentially be affected by VAP, in accordance with (3), we adjusted for SOFA score and antibiotic treatment (and total number of treated days up to) two days before each considered time wave of possible occurrence of VAP.

The model included a flexible functional form of all continuous covariates (a restricted cubic spline with 3 knots (***) whenever feasible, or 2 knots (**) otherwise) and additional time-transformed functions of covariates (the product of log(time-1) and the covariate) for which a smoothed function of the scaled Schoenfeld residuals over time indicated clear violations of the proportional hazards assumption (indicated with a single asterisk (*) in the list below).

Baseline and admission characteristics

- Gender
- Age at ICU admission (***)
- Admission category (medical, emergency surgery or scheduled surgery)
- Admission year (2013, 2014, 2015, 2016, 2017)

- APACHE II score (***)
- Updated Charlson comorbidity index (**)
- Antibiotic therapy at baseline (i.e. during the first two days at the ICU)
- Total SOFA score at baseline (i.e. at day 1 = the second calendar day at the ICU) (***)

Time-varying covariates including daily updated disease severity and interventions

- Daily total SOFA score two days before possible occurrence of VAP (***)
- Daily evolution in total SOFA score (i.e. difference in total SOFA score two vs three days before possible occurrence of VAP) (***)
- Daily updated treatment limitation decisions (TLDs) (code 0, 1, 2 or higher)
- Daily indicator of antibiotic therapy two days before possible occurrence of VAP
- Daily indicator of
    - mechanical ventilation (*)
    - administration of vasoactive agents
    - enteral feeding
    - administration of corticosteroids (>0.5 ml/kg)
    - hemodialysis
    - presence of a tracheotomy tube
    - suspected or confirmed bacterial abdominal infection
    - suspected or confirmed bacterial catheter-related infection
    - suspected or confirmed bacterial respiratory infection (*)
    - suspected or confirmed bacterial urinary tract infection
    - suspected or confirmed other bacterial infections
    - suspected or confirmed fungal infection

  1 day before possible occurrence of VAP

- Daily updated cumulative number of days exposed to antibiotic therapy up to two days before possible occurrence of VAP
- Daily updated cumulative number of days exposed to
    - mechanical ventilation
    - administration of vasoactive agents
    - enteral feeding
    - administration of corticosteroids (>0.5 ml/kg)
    - hemodialysis
    - presence of a tracheotomy tube
    - suspected or confirmed bacterial abdominal infection
    - suspected or confirmed bacterial catheter-related infection
    - suspected or confirmed bacterial respiratory infection
    - suspected or confirmed bacterial urinary tract infection
    - suspected or confirmed other bacterial infections
    - suspected or confirmed fungal infection

  up to 1 day before possible occurrence of VAP

Figure E2 and Figure E3 display the results of the final time-dependent Cox model. Figure E4 displays the distribution of IP weights assigned to VAP-free patients as a function of day since ICU admission.

**Assessment of covariate balance**

At every time wave, time-dependent IP weights ideally restore covariate balance across future exposures, conditional on the past exposure history. Because we aim to compare the counterfactual VAP-free cumulative incidence curve with the observed cumulative incidence curve (rather than another counterfactual curve), we focused on covariate balance between patients that were at risk of VAP at the beginning of each day (i.e. had remained hospitalized and without VAP (at least) up until the previous day) and a subgroup of those patients who died or were discharged without VAP or remained hospitalized without VAP until the end of that day (i.e. those patients whose weighted deaths that day contributed to the 'counterfactual' cumulative incidence curve).

Figure E5 displays covariate balance at days 2, 4, 8, 12 and 24, before and after IP weighting. These plots allow to assess extent to which IP weighting succeeded to accommodate covariate imbalances (summarized by standardized mean differences for continuous covariates or raw mean differences for binary covariates) due to selection of the latter from the former group of hospitalized patients on each day.

In theory, covariate balance should be checked at every single time window at which we considered incident VAP cases (i.e. daily, up to day 60 from ICU admission). However, this becomes quite cumbersome with an increasing number of time waves. We have therefore chosen to restrict assessment of covariate balance to a limited number of time waves.

## References


1. De Bus L, Saerens L, Gadeyne B, Boelens J, Claeys G, De Waele JJ, et al. Development of antibiotic treatment algorithms based on local ecology and respiratory surveillance cultures to restrict the use of broad-spectrum antimicrobial drugs in the treatment of hospital-acquired pneumonia in the intensive care unit: a retrospecti. Crit care [Internet]. 2014;18(4):R152. Available from: http://ccforum.com/content/18/4/R152
2. De Bus L, Diet G, Gadeyne B, Leroux-Roels I, Claeys G, Steurbaut K, et al. Validity analysis of a unique infection surveillance system in the intensive care unit by analysis of a data warehouse built through a workflow-integrated software application. J Hosp Infect [Internet]. 2014;87(3):159–64. Available from: http://dx.doi.org/10.1016/j.jhin.2014.03.010
3. Bekaert M, Timsit J-F, Vansteelandt S, Depuydt P, Vésin A, Garrouste-Orgeas M, et al. Attributable mortality of ventilator-associated pneumonia: A reappraisal using causal analysis. Am J Respir Crit Care Med. 2011;184(10):1133–9.
4. Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, et al. Updating and validating the charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol. 2011;173(6):676–82.
5. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med [Internet]. 1985 Oct;13(10):818–29. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3928249
6. De Bus L, Gadeyne B, Steen J, Boelens J, Claeys G, Benoit D, et al. A complete and multifaceted overview of antibiotic use and infection diagnosis in the intensive care unit: results from a prospective four-year registration. Crit Care [Internet]. 2018 Dec

29;22(1):241. Available from: https://ccforum.biomedcentral.com/articles/10.1186/s13054-018-2178-7

7. Piers RD, Benoit DD, Schrauwen WJ, Van Den Noortgate NJ. DO-not-resuscitate decisions in a large tertiary hospital: Differences between wards and results of a hospital-wide intervention. Acta Clin Belg. 2011;66(2):116–22.
8. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med [Internet]. 1996 Jul;22(7):707–10. Available from: http://link.springer.com/10.1007/BF01709751
9. Houthooft R, Ruyssinck J, van der Herten J, Stijven S, Couckuyt I, Gadeyne B, et al. Predictive modelling of survival and length of stay in critically ill patients using sequential organ failure scores. Artif Intell Med [Internet]. 2015;63(3):191–207. Available from: http://dx.doi.org/10.1016/j.artmed.2014.12.009
10. Hernán MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. Am J Epidemiol. 2016;183(8):758–64.
11. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ [Internet]. 2016 Oct 12;355:i4919. Available from: http://www.bmj.com/lookup/doi/10.1136/bmj.i4919
12. Steen J, Vansteelandt S, Decruyenaere J. Handling time-dependent exposures and confounders when estimating attributable fractions -- bridging the gap between multi state and counterfactual modeling. (in preparation)
13. von Cube M, Schumacher M, Bailly S, Timsit J, Lepape A, Savey A, et al. The population-attributable fraction for time-dependent exposures and competing risks—A discussion on estimands. Stat Med [Internet]. 2019 Jun 4;(May 2018):sim.8208.

Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/sim.8208

14. Schumacher M, Wangler M, Wolkewitz M, Beyersmann J. Attributable mortality due to nosocomial infections: A simple and useful application of multistate models. Methods Inf Med. 2007;46(5):595–600.

15. Arjas E, Eerola M. On predictive causality in longitudinal studies. J Stat Plan Inference. 1993;34(3):361–86.

16. Keiding N, Filiberti M, Esbjerg S, Robins JM, Jacobsen N. The graft versus leukemia effect after bone marrow transplantation: A case study using structural nested failure time models. Biometrics. 1999;55(1):23–8.

17. Keiding N, Klein JP, Horowitz MM. Multi-state models and outcome prediction in bone marrow transplantation. Stat Med. 2001;20(12):1871–85.

18. Klein JP, Keiding N, Copelan EA. Plotting summary predictions in multistate survival models: Probabilities of relapse and death in remission for bone marrow transplantation patients. Stat Med [Internet]. 1993 Dec 30;12(24):2315–32. Available from: http://doi.wiley.com/10.1002/sim.4780122408

19. Robins J, Hernan M. Estimation of the causal effects of time-varying exposures. In: Fitzmaurice G, Davidian M, Verbeke G, Molenberghs G, editors. Longitudinal Data Analysis [Internet]. Boca Raton, Florida: Chapman and Hall/CRC; 2008. p. 553–99. Available from: http://www.crcnetbase.com/doi/abs/10.1201/9781420011579.ch23

20. Hernán MA, Robins JM. Causal Inference: What If. Boca Raton: Chapman & Hall/CRC; 2020.

21. Hernán MA. Does water kill? A call for less casual causal inferences. Ann Epidemiol [Internet]. 2016;26(10):674–80. Available from: http://dx.doi.org/10.1016/j.annepidem.2016.08.016

22. Pearl J. Does Obesity Shorten Life? Or is it the Soda? On Non-manipulable Causes. J

Causal Inference [Internet]. 2018 Aug 24; Available from: http://www.degruyter.com/view/j/jci.ahead-of-print/jci-2018-2001/jci-2018-2001.xml

23. Hernán MA, Taubman SL. Does obesity shorten life? The importance of well-defined interventions to answer causal questions. Int J Obes (Lond) [Internet]. 2008;32 Suppl 3:S8–14. Available from: http://www.nature.com/doifinder/10.1038/ijo.2008.82

Figure legends

Figure E1.

Simplified causal diagram (*A*) (also available as an interactive DAGitty diagram from this webpage: http://dagitty.net/mdJm-Ys) and modified causal diagram after IP weighting (*B*) (also available from this webpage: http://dagitty.net/dags.html?id=ebuxWi).

Figure E2.

Point and 95% confidence interval estimates of adjusted hazard ratios of all categorical variables in the final time-dependent Cox model for daily risk of acquiring VAP.

Figure E3.

Point and 95% confidence interval estimates of adjusted hazard ratios of all continuous variables in the final time-dependent Cox model for daily risk of acquiring VAP.

Figure E4.

Distribution of inverse probability (IP) weights assigned to VAP-free patients as a function of day since ICU admission.

Figure E5.

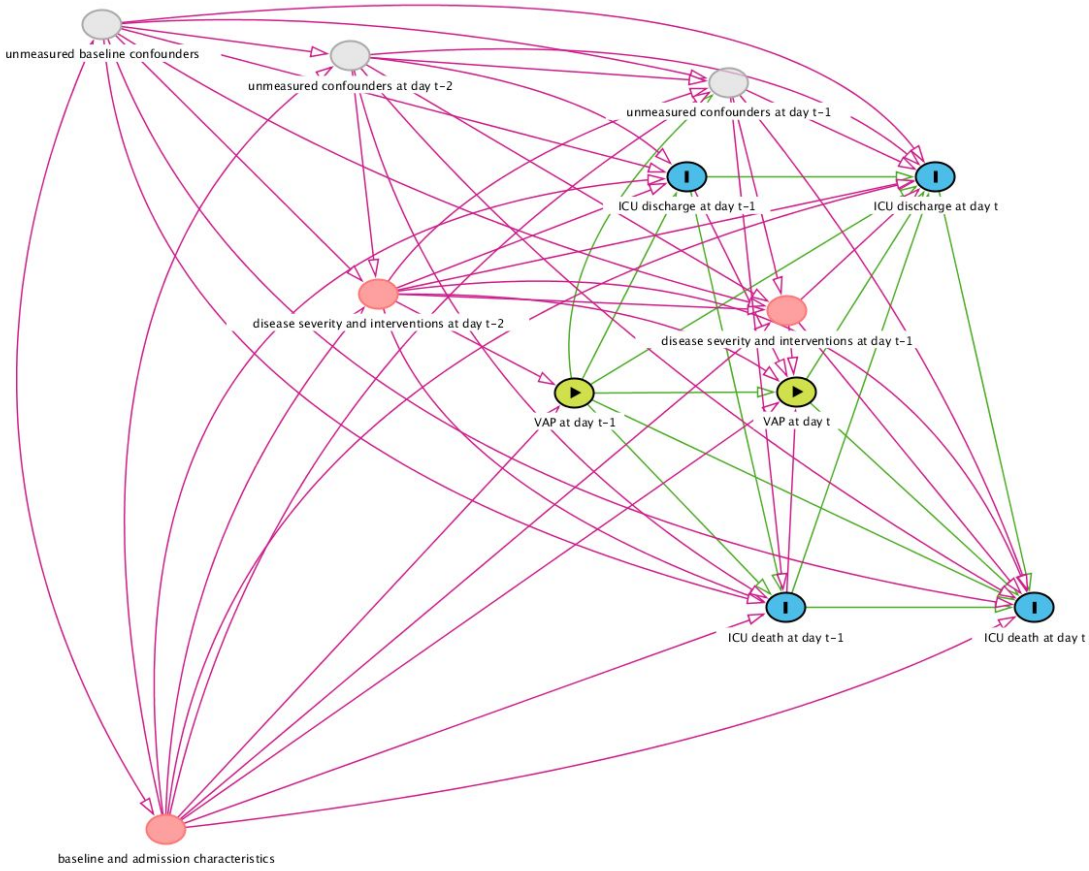
Covariate balance before and after IP weighting at days 2, 4, 8, 12 and 24 between patients at risk of VAP at the beginning of each day (i.e. had remained hospitalized and without VAP (at least) up until the previous day) and a subgroup of those patients who died or were discharged without VAP or remained hospitalized without VAP until the end of that day.

Figure E6.

Comparison of results for estimating the time-dependent population-attributable fraction (PAF) of intensive care unit (ICU) mortality due to ventilator-associated pneumonia (VAP) based on an unadjusted competing risk (CR) analysis (approach 3 in the main text; *A*), a CR analysis that adjusts for gender, age and SOFA score at ICU admission (*B*), a CR analysis that adjusts for an extended set of admission characteristics including admission year, admission category, updated Charlson comorbidity index, APACHE II score and antibiotic treatment at ICU admission (*C*), and a CR analysis that additionally adjusts for time-dependent confounding (approach 4 in the main text; *D*). Upper panels: observed cumulative incidence of ICU mortality (*black curves*) and estimated counterfactual VAP-free cumulative incidence of ICU mortality (*grey curves*). Lower panels: estimated PAF of ICU death due to VAP (*solid lines*) and 95% pointwise confidence intervals (*shaded areas*).

Figure E1.

**(A)**


unmeasured baseline confounders
unmeasured confounders at day t−2
unmeasured confounders at day t−1
ICU discharge at day t−1
ICU discharge at day t
disease severity and interventions at day t−2
disease severity and interventions at day t−1
VAP at day t−1
VAP at day t
ICU death at day t−1
ICU death at day t
baseline and admission characteristics

**(B)**

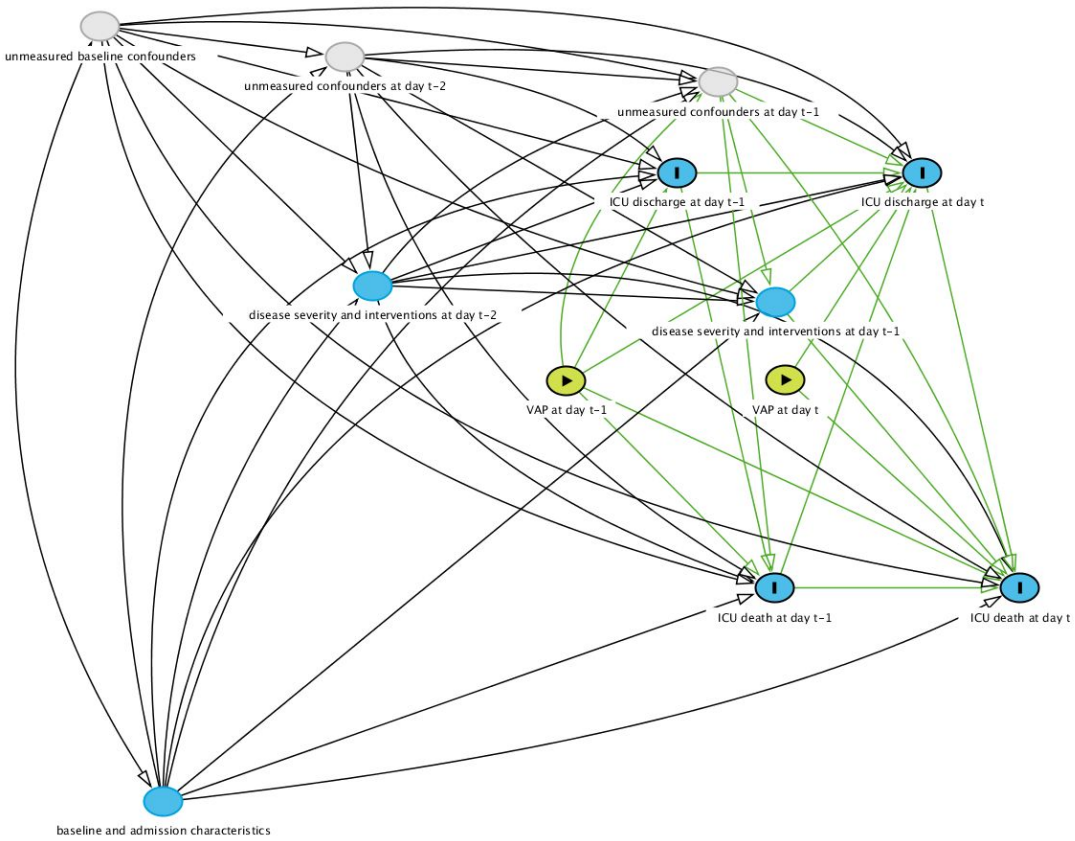

unmeasured baseline confounders
unmeasured confounders at day t-2
unmeasured confounders at day t-1
ICU discharge at day t-1
ICU discharge at day t
disease severity and interventions at day t-2
disease severity and interventions at day t-1
VAP at day t-1
VAP at day t
ICU death at day t-1
ICU death at day t
baseline and admission characteristics

Figure E2.

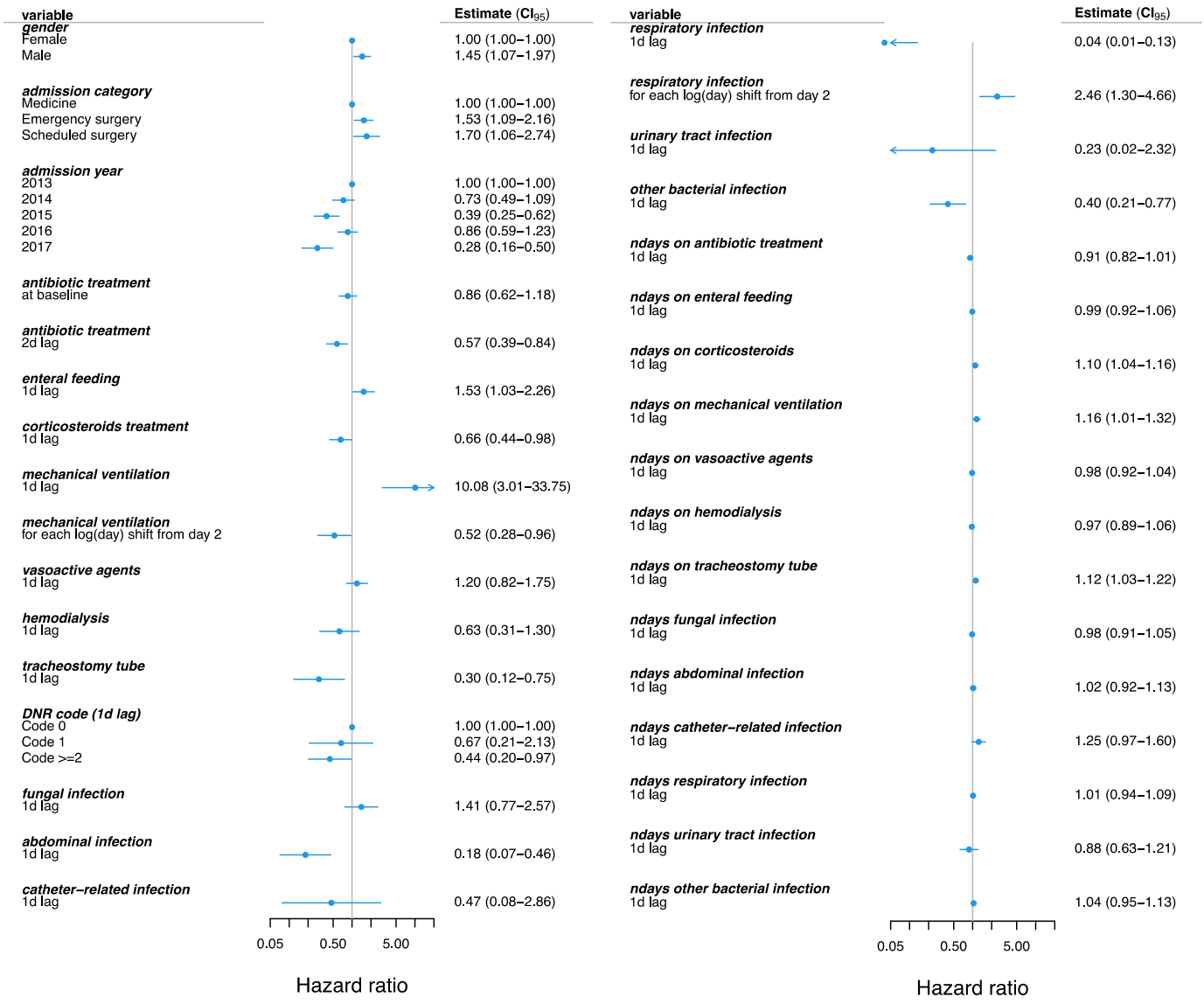

variable
Estimate (CI95)
gender
Female 1.00 (1.00–1.00)
Male 1.45 (1.07–1.97)
admission category
Medicine 1.00 (1.00–1.00)
Emergency surgery 1.53 (1.09–2.16)
Scheduled surgery 1.70 (1.06–2.74)
admission year
2013 1.00 (1.00–1.00)
2014 0.73 (0.49–1.09)
2015 0.39 (0.25–0.62)
2016 0.86 (0.59–1.23)
2017 0.28 (0.16–0.50)
antibiotic treatment
at baseline 0.86 (0.62–1.18)
antibiotic treatment
2d lag 0.57 (0.39–0.84)
enteral feeding
1d lag 1.53 (1.03–2.26)
corticosteroids treatment
1d lag 0.66 (0.44–0.98)
mechanical ventilation
1d lag 10.08 (3.01–33.75)
mechanical ventilation
for each log(day) shift from day 2 0.52 (0.28–0.96)
vasoactive agents
1d lag 1.20 (0.82–1.75)
hemodialysis
1d lag 0.63 (0.31–1.30)
tracheostomy tube
1d lag 0.30 (0.12–0.75)
DNR code (1d lag)
Code 0 1.00 (1.00–1.00)
Code 1 0.67 (0.21–2.13)
Code >=2 0.44 (0.20–0.97)
fungal infection
1d lag 1.41 (0.77–2.57)
abdominal infection
1d lag 0.18 (0.07–0.46)
catheter–related infection
1d lag 0.47 (0.08–2.86)
0.05
0.50
5.00
Hazard ratio
variable
Estimate (CI95)
respiratory infection
1d lag 0.04 (0.01–0.13)
respiratory infection
for each log(day) shift from day 2 2.46 (1.30–4.66)
urinary tract infection
1d lag 0.23 (0.02–2.32)
other bacterial infection
1d lag 0.40 (0.21–0.77)
ndays on antibiotic treatment
1d lag 0.91 (0.82–1.01)
ndays on enteral feeding
1d lag 0.99 (0.92–1.06)
ndays on corticosteroids
1d lag 1.10 (1.04–1.16)
ndays on mechanical ventilation
1d lag 1.16 (1.01–1.32)
ndays on vasoactive agents
1d lag 0.98 (0.92–1.04)
ndays on hemodialysis
1d lag 0.97 (0.89–1.06)
ndays on tracheostomy tube
1d lag 1.12 (1.03–1.22)
ndays fungal infection
1d lag 0.98 (0.91–1.05)
ndays abdominal infection
1d lag 1.02 (0.92–1.13)
ndays catheter–related infection
1d lag 1.25 (0.97–1.60)
ndays respiratory infection
1d lag 1.01 (0.94–1.09)
ndays urinary tract infection
1d lag 0.88 (0.63–1.21)
ndays other bacterial infection
1d lag 1.04 (0.95–1.13)
0.05
0.50
5.00
Hazard ratio

Figure E3.

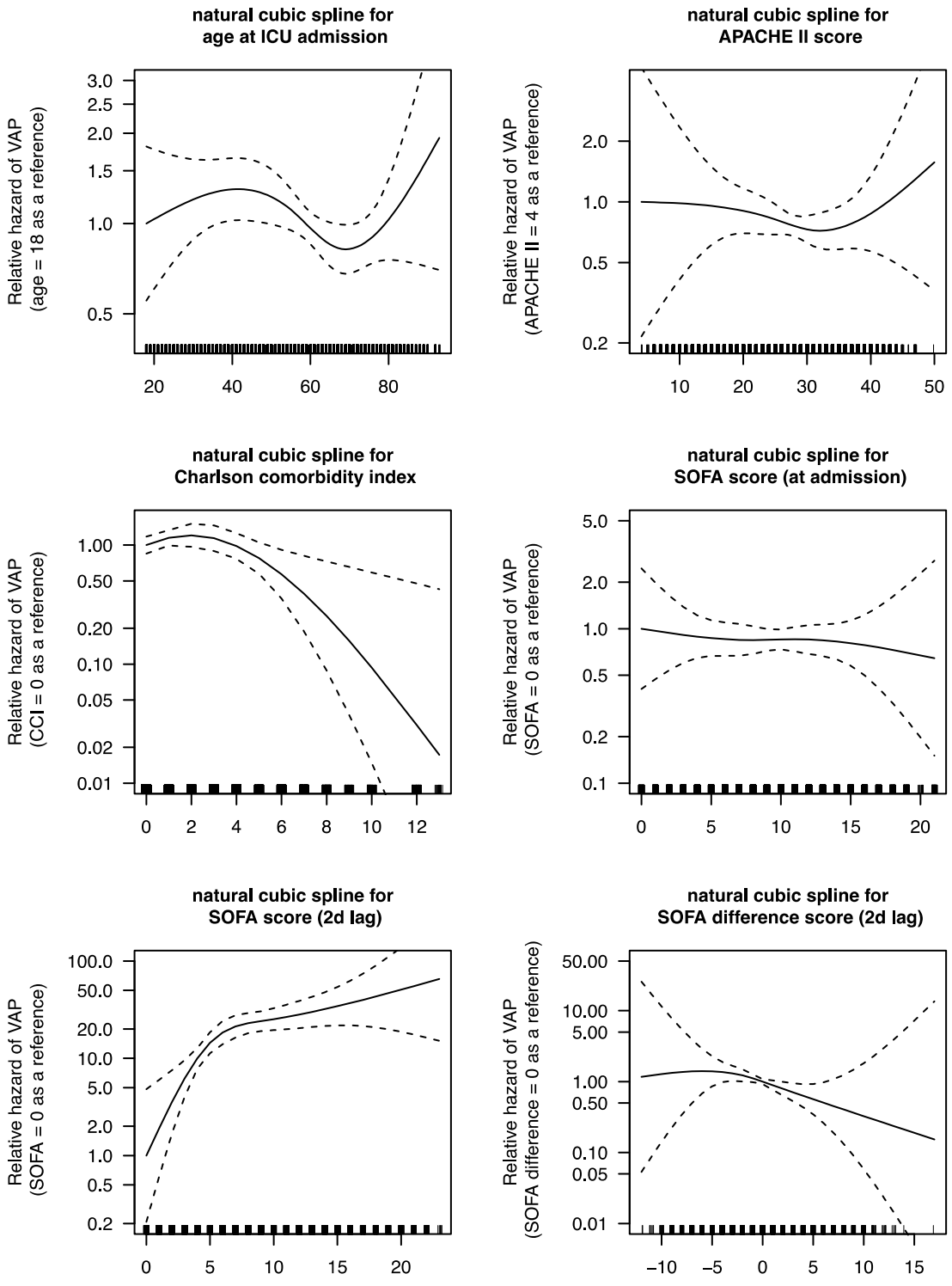

natural cubic spline for
age at ICU admission
Relative hazard of VAP
(age = 18 as a reference)
3.0
2.5
2.0
1.5
1.0
0.5
20
40
60
80
natural cubic spline for
APACHE II score
Relative hazard of VAP
(APACHE II = 4 as a reference)
2.0
1.0
0.5
0.2
10
20
30
40
50
natural cubic spline for
Charlson comorbidity index
Relative hazard of VAP
(CCI = 0 as a reference)
1.00
0.50
0.20
0.10
0.05
0.02
0.01
0
2
4
6
8
10
12
natural cubic spline for
SOFA score (at admission)
Relative hazard of VAP
(SOFA = 0 as a reference)
5.0
2.0
1.0
0.5
0.2
0.1
0
5
10
15
20
natural cubic spline for
SOFA score (2d lag)
Relative hazard of VAP
(SOFA = 0 as a reference)
100.0
50.0
20.0
10.0
5.0
2.0
1.0
0.5
0.2
0
5
10
15
20
natural cubic spline for
SOFA difference score (2d lag)
Relative hazard of VAP
(SOFA difference = 0 as a reference)
50.00
10.00
5.00
1.00
0.50
0.10
0.05
0.01
−10
−5
0
5
10
15

Figure E4.

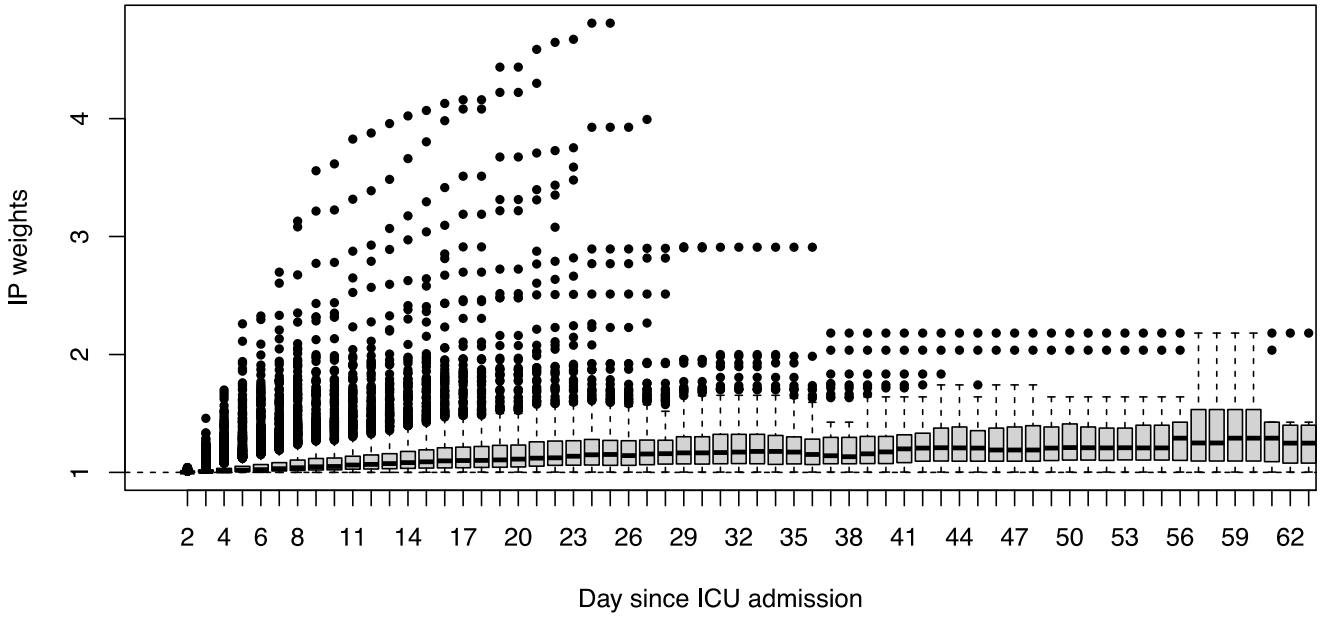
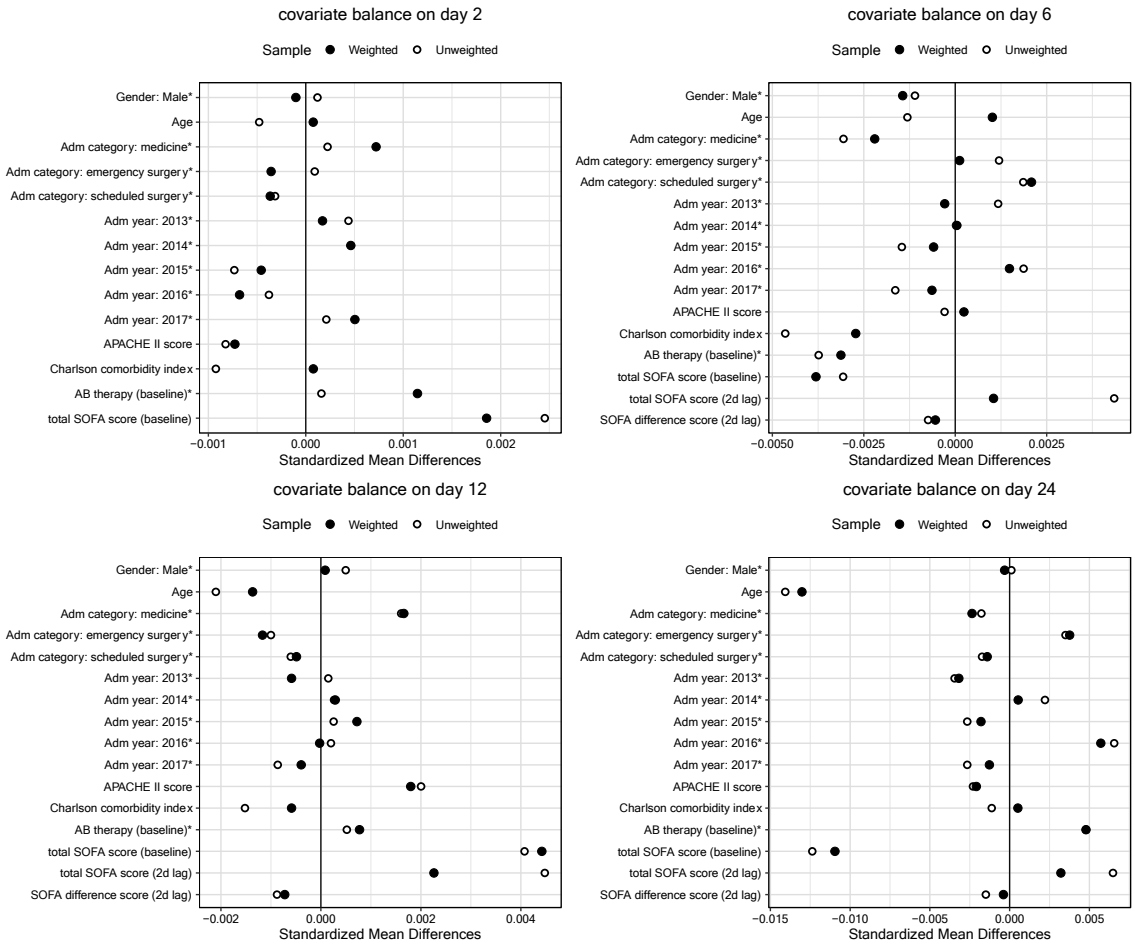
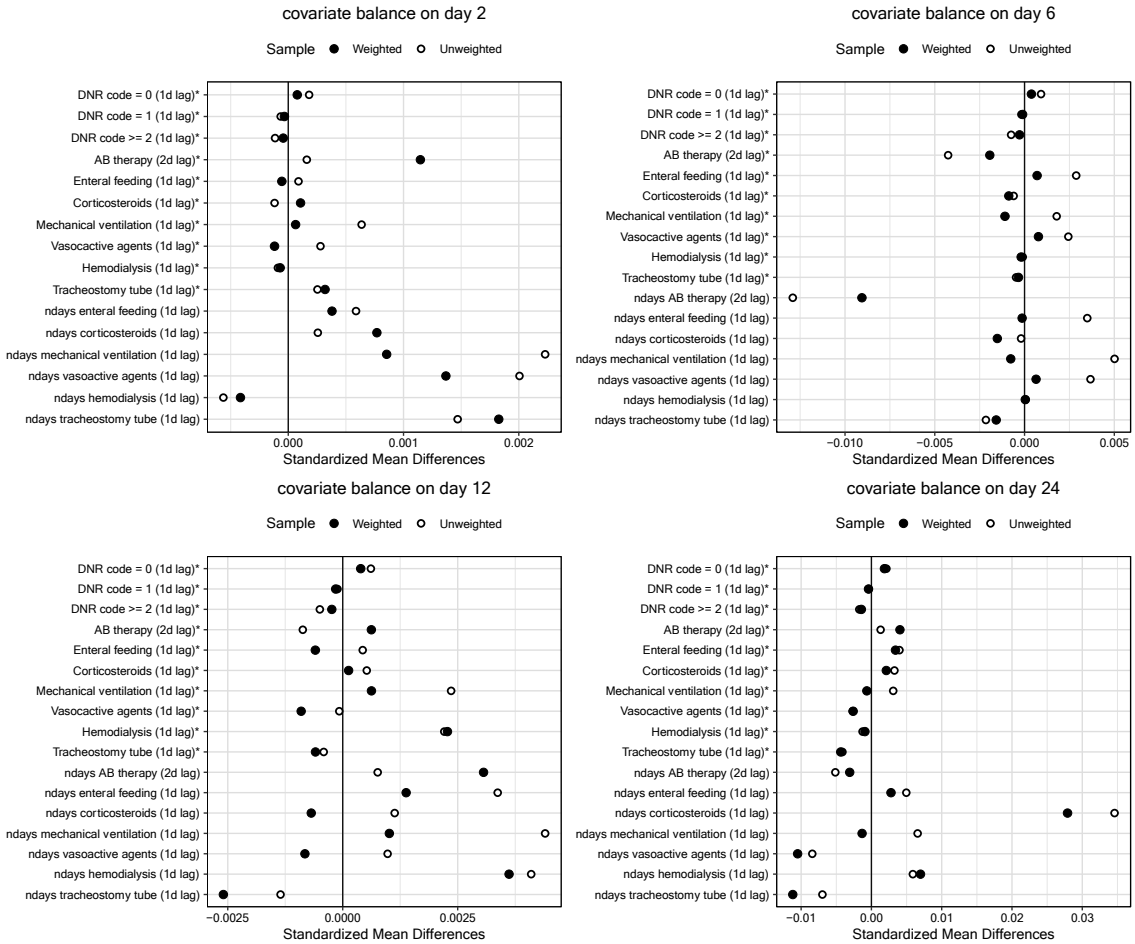

IP weights
1
2
3
4
2 4 6 8 11 14 17 20 23 26 29 32 35 38 41 44 47 50 53 56 59 62
Day since ICU admission

Figure E5.


covariate balance on day 2
Sample Weighted Unweighted
Gender: Male*
Age
Adm category: medicine*
Adm category: emergency surgery*
Adm category: scheduled surgery*
Adm year: 2013*
Adm year: 2014*
Adm year: 2015*
Adm year: 2016*
Adm year: 2017*
APACHE II score
Charlson comorbidity index
AB therapy (baseline)*
total SOFA score (baseline)
−0.001 0.000 0.001 0.002
Standardized Mean Differences
covariate balance on day 6
Sample Weighted Unweighted
Gender: Male*
Age
Adm category: medicine*
Adm category: emergency surgery*
Adm category: scheduled surgery*
Adm year: 2013*
Adm year: 2014*
Adm year: 2015*
Adm year: 2016*
Adm year: 2017*
APACHE II score
Charlson comorbidity index
AB therapy (baseline)*
total SOFA score (baseline)
total SOFA score (2d lag)
SOFA difference score (2d lag)
−0.0050 −0.0025 0.0000 0.0025
Standardized Mean Differences
covariate balance on day 12
Sample Weighted Unweighted
Gender: Male*
Age
Adm category: medicine*
Adm category: emergency surgery*
Adm category: scheduled surgery*
Adm year: 2013*
Adm year: 2014*
Adm year: 2015*
Adm year: 2016*
Adm year: 2017*
APACHE II score
Charlson comorbidity index
AB therapy (baseline)*
total SOFA score (baseline)
total SOFA score (2d lag)
SOFA difference score (2d lag)
−0.002 0.000 0.002 0.004
Standardized Mean Differences
covariate balance on day 24
Sample Weighted Unweighted
Gender: Male*
Age
Adm category: medicine*
Adm category: emergency surgery*
Adm category: scheduled surgery*
Adm year: 2013*
Adm year: 2014*
Adm year: 2015*
Adm year: 2016*
Adm year: 2017*
APACHE II score
Charlson comorbidity index
AB therapy (baseline)*
total SOFA score (baseline)
total SOFA score (2d lag)
SOFA difference score (2d lag)
−0.015 −0.010 −0.005 0.000 0.005
Standardized Mean Differences


covariate balance on day 2
Sample Weighted Unweighted
DNR code = 0 (1d lag)*
DNR code = 1 (1d lag)*
DNR code >= 2 (1d lag)*
AB therapy (2d lag)*
Enteral feeding (1d lag)*
Corticosteroids (1d lag)*
Mechanical ventilation (1d lag)*
Vasocactive agents (1d lag)*
Hemodialysis (1d lag)*
Tracheostomy tube (1d lag)*
ndays enteral feeding (1d lag)
ndays corticosteroids (1d lag)
ndays mechanical ventilation (1d lag)
ndays vasoactive agents (1d lag)
ndays hemodialysis (1d lag)
ndays tracheostomy tube (1d lag)
0.000
0.001
0.002
Standardized Mean Differences
covariate balance on day 6
Sample Weighted Unweighted
DNR code = 0 (1d lag)*
DNR code = 1 (1d lag)*
DNR code >= 2 (1d lag)*
AB therapy (2d lag)*
Enteral feeding (1d lag)*
Corticosteroids (1d lag)*
Mechanical ventilation (1d lag)*
Vasocactive agents (1d lag)*
Hemodialysis (1d lag)*
Tracheostomy tube (1d lag)*
ndays AB therapy (2d lag)
ndays enteral feeding (1d lag)
ndays corticosteroids (1d lag)
ndays mechanical ventilation (1d lag)
ndays vasoactive agents (1d lag)
ndays hemodialysis (1d lag)
ndays tracheostomy tube (1d lag)
−0.010
−0.005
0.000
0.005
Standardized Mean Differences
covariate balance on day 12
Sample Weighted Unweighted
DNR code = 0 (1d lag)*
DNR code = 1 (1d lag)*
DNR code >= 2 (1d lag)*
AB therapy (2d lag)*
Enteral feeding (1d lag)*
Corticosteroids (1d lag)*
Mechanical ventilation (1d lag)*
Vasocactive agents (1d lag)*
Hemodialysis (1d lag)*
Tracheostomy tube (1d lag)*
ndays AB therapy (2d lag)
ndays enteral feeding (1d lag)
ndays corticosteroids (1d lag)
ndays mechanical ventilation (1d lag)
ndays vasoactive agents (1d lag)
ndays hemodialysis (1d lag)
ndays tracheostomy tube (1d lag)
−0.0025
0.0000
0.0025
Standardized Mean Differences
covariate balance on day 24
Sample Weighted Unweighted
DNR code = 0 (1d lag)*
DNR code = 1 (1d lag)*
DNR code >= 2 (1d lag)*
AB therapy (2d lag)*
Enteral feeding (1d lag)*
Corticosteroids (1d lag)*
Mechanical ventilation (1d lag)*
Vasocactive agents (1d lag)*
Hemodialysis (1d lag)*
Tracheostomy tube (1d lag)*
ndays AB therapy (2d lag)
ndays enteral feeding (1d lag)
ndays corticosteroids (1d lag)
ndays mechanical ventilation (1d lag)
ndays vasoactive agents (1d lag)
ndays hemodialysis (1d lag)
ndays tracheostomy tube (1d lag)
−0.01
0.00
0.01
0.02
0.03
Standardized Mean Differences

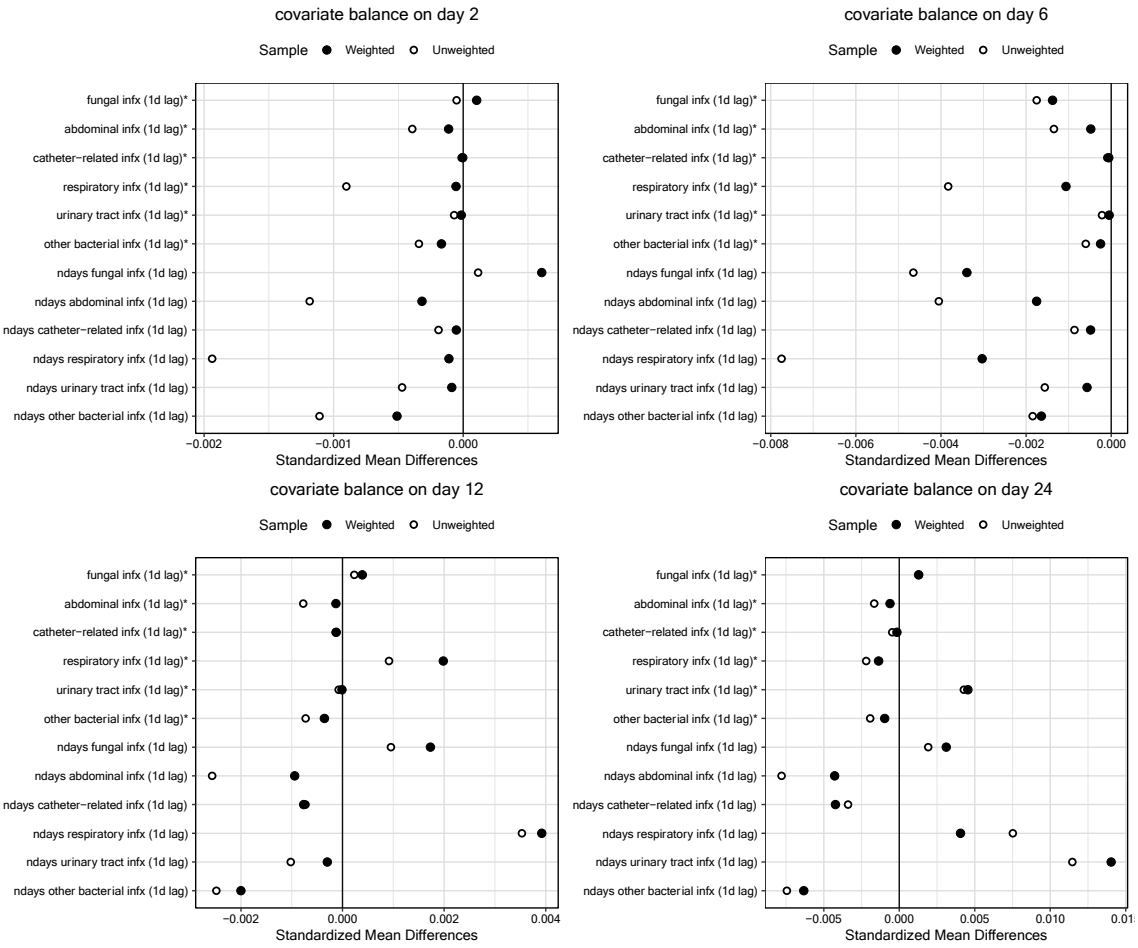
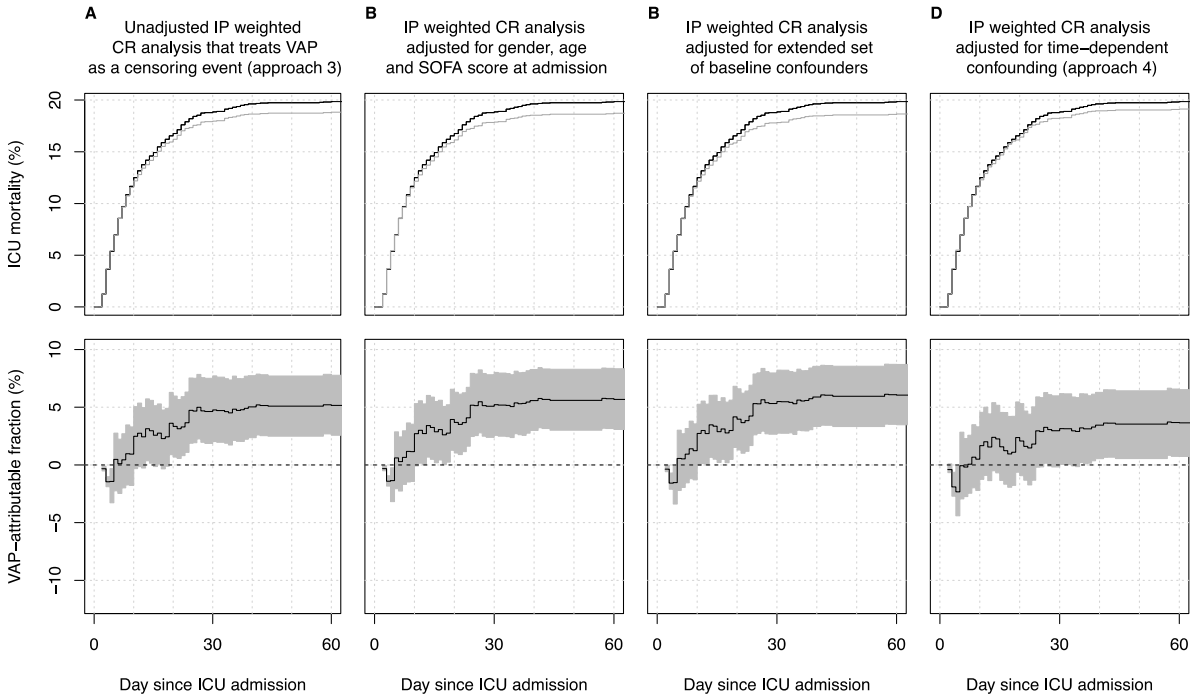

covariate balance on day 2
Sample Weighted Unweighted
fungal infx (1d lag)*
abdominal infx (1d lag)*
catheter−related infx (1d lag)*
respiratory infx (1d lag)*
urinary tract infx (1d lag)*
other bacterial infx (1d lag)*
ndays fungal infx (1d lag)
ndays abdominal infx (1d lag)
ndays catheter−related infx (1d lag)
ndays respiratory infx (1d lag)
ndays urinary tract infx (1d lag)
ndays other bacterial infx (1d lag)
−0.002
−0.001
0.000
Standardized Mean Differences
covariate balance on day 6
Sample Weighted Unweighted
fungal infx (1d lag)*
abdominal infx (1d lag)*
catheter−related infx (1d lag)*
respiratory infx (1d lag)*
urinary tract infx (1d lag)*
other bacterial infx (1d lag)*
ndays fungal infx (1d lag)
ndays abdominal infx (1d lag)
ndays catheter−related infx (1d lag)
ndays respiratory infx (1d lag)
ndays urinary tract infx (1d lag)
ndays other bacterial infx (1d lag)
−0.008
−0.006
−0.004
−0.002
0.000
Standardized Mean Differences
covariate balance on day 12
Sample Weighted Unweighted
fungal infx (1d lag)*
abdominal infx (1d lag)*
catheter−related infx (1d lag)*
respiratory infx (1d lag)*
urinary tract infx (1d lag)*
other bacterial infx (1d lag)*
ndays fungal infx (1d lag)
ndays abdominal infx (1d lag)
ndays catheter−related infx (1d lag)
ndays respiratory infx (1d lag)
ndays urinary tract infx (1d lag)
ndays other bacterial infx (1d lag)
−0.002
0.000
0.002
0.004
Standardized Mean Differences
covariate balance on day 24
Sample Weighted Unweighted
fungal infx (1d lag)*
abdominal infx (1d lag)*
catheter−related infx (1d lag)*
respiratory infx (1d lag)*
urinary tract infx (1d lag)*
other bacterial infx (1d lag)*
ndays fungal infx (1d lag)
ndays abdominal infx (1d lag)
ndays catheter−related infx (1d lag)
ndays respiratory infx (1d lag)
ndays urinary tract infx (1d lag)
ndays other bacterial infx (1d lag)
−0.005
0.000
0.005
0.010
Standardized Mean Differences

Figure E6.


A
Unadjusted IP weighted CR analysis that treats VAP as a censoring event (approach 3)
B
IP weighted CR analysis adjusted for gender, age and SOFA score at admission
B
IP weighted CR analysis adjusted for extended set of baseline confounders
D
IP weighted CR analysis adjusted for time−dependent confounding (approach 4)
ICU mortality (%)
0
5
10
15
20
VAP−attributable fraction (%)
−10
−5
0
5
10
0
30
60
Day since ICU admission