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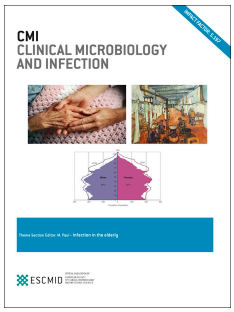

Modifiable and non-modifiable risk factors for non-ventilator-associated hospital-acquired pneumonia (nvHAP) identified in a retrospective cohort study

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PII: S1198-743X(22)00267-1

DOI: https://doi.org/10.1016/j.cmi.2022.05.011

Reference: CMI 2948

To appear in: *Clinical Microbiology and Infection*

Received Date: 15 November 2021

Revised Date: 2 May 2022

Accepted Date: 8 May 2022

Please cite this article as: Kachalov VN, Kuster SP, Balakrishna S, Schreiber PW, Jakob W, Sax H, Kouyos RD, Wolfensberger A, Modifiable and non-modifiable risk factors for non-ventilator-associated hospital-acquired pneumonia (nvHAP) identified in a retrospective cohort study, *Clinical Microbiology and Infection*, https://doi.org/10.1016/j.cmi.2022.05.011.

TITLE PAGE

Modifiable and non-modifiable risk factors for non-ventilator-associated hospital-acquired pneumonia (nvHAP) identified in a retrospective cohort study

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Submitted to: CMI

Wordcount: (2500 /2500)

Conflicts of interest: none to declare for all authors.

Keywords: Hospital-acquired pneumonia, risk factors, healthcare-associated infections, infection prevention, pneumonia

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ABSTRACT (244/250 words)

Objectives: Hospital-acquired pneumonia in non-ventilated patients (nvHAP) belongs to the most common healthcare-associated infections. This study aimed to investigate risk factors for nvHAP in patients outside the intensive care unit, focusing on modifiable risk factors.

Methods: All inpatients admitted to an academic teaching hospital in Switzerland between 2017 and 2018 were included. NvHAP was defined according to European Centre for Disease Prevention and Control criteria. Patient days during and after ICU stay were excluded. Candidate risk factors - both constant and time-varying - were included in uni- and multivariable Cox proportional hazards models. The decay ratio and the characteristic time of influence of HRs was estimated by adopting a linear decay in the Cox model.

Results: A total of 66,001 hospitalizations with 314 (0.48%) nvHAP and 471,401 patient days were included. Median age was 57 years (interquartile range: 38-71 years) and 32,253 (48.9%) patients were male. Among non-modifiable risk factors, age (adjusted-HR 2.66 for age ≥60 years, 95%CI 1.59-4.45) and male sex (aHR 1.71, 95%CI 1.34-2.18) were independently associated with nvHAP. Time-varying exposures showing strongest independent association with nvHAP were tube feeding (aHR 3.24, 95%CI 2.17-4.83), impaired consciousness (aHR 2.32, 95%CI 1.63-3.31), and severely impaired activity and mobility (aHR 2.06, 95%CI 1.50-2.84). The association with nvHAP decayed within 7.1 – 13.2 days after these exposures ended.

Conclusions: The risk for nvHAP varies with time, depending on the patient's medical condition and medical interventions. Several risk factors for nvHAP represent potential targets for specific prevention measures.

INTRODUCTION

Healthcare-associated infections (HAI) are associated with morbidity, mortality, and substantial hospital cost (1, 2). Pneumonia and lower respiratory tract infections are the most common HAI, and more than 60% of pneumonia affect non-ventilated patients (3, 4). Multiple studies performed to identify risk factors for nosocomial pneumonia in general, including both ventilated and non-ventilated patients, resulted in identifying intubation as the most important risk factors for hospital-acquired pneumonia (5-7).

Some authors specifically assessed risk factors for pneumonia in the non-ventilated patient population (8-12). Until now, most studies investigating nvHAP risk factors focused on demographic data or co-morbidities. These factors are generally non-modifiable within the period of one hospitalization. On the other hand, some factors potentially associated with nvHAP might be avoidable or addressable by intervention, like procedures (e.g., sedation, surgery) and medical conditions (e.g., pain, delirium, or dysphagia). Yet, only a few authors evaluated modifiable or potentially modifiable risk factors such as depression of consciousness and immobilization (8, 9).

As knowledge about risk factors for nvHAP is key to allow focusing targeted prevention measures on patients at the highest risk, we aimed to identify both time-varying and non-time-varying risk factors for non-fungal nvHAP. For time-varying factors, we aimed to assess the time during which a risk factor is relevant after exposure stopped, hypothesizing that the association is of limited temporal connection. As most patients develop nvHAP on general wards or intermediate care units (13), we focused our study on patients outside the intensive care unit (ICU).

METHODS

Study setting and patient population

This retrospective cohort study was conducted at the University Hospital of Zurich (UHZ), Switzerland, a 950-bed tertiary-care teaching hospital covering all medical specialties except pediatrics and orthopedics. All adult inpatients (≥18 years) who were discharged or deceased in 2017 and 2018 were included. The study was conducted as part of a quality improvement project and waived from the Zurich Cantonal Ethics Commission from the necessity for a formal ethical evaluation (Req 2017-00708).

Definition of nvHAP and selection of risk factor candidate variables

Hospital-acquired pneumonia was defined according to European Centre for Disease Prevention and Control (ECDC) definitions (14) (**Appendix** ECDC definitions). Pneumonia was defined as hospital-acquired when symptoms start ≥48 hours after admission or <48 hours after discharge (**Figure 1 A**). If an invasive respiratory device was present in the 48 hours preceding symptom onset (except for surgery only), the pneumonia was considered ventilator-acquired pneumonia (VAP) and was not subject of this study (**Figure 1 B**). Fungal HAP, defined as HAP fulfilling the criteria for “possible”, “probable”, or “proven” fungal pneumonia according to EORTC/MSG (15), were excluded. NvHAP onset was defined as the day of first symptoms. Surveillance of nvHAP was conducted retrospectively after the discharge of patients by using a validated semi-automated surveillance system for nvHAP (13). Sensitivity of the semi-automated surveillance was 97.5% (CI 93.7 – 99.3%) in a validation sample consisting of 637 patients with HAP according to discharge diagnostic codes.

Candidate risk factors for nvHAP were a priori defined according to scientific literature and expert opinion. Both time-varying (i.e. potentially modifiable) risk factor candidate variables, extracted from electronic medical records per day, and non-time-varying (i.e. non-modifiable within the period of one hospitalization) exposures were included (see **Appendix Table 1**). Missing entries of daily nursing assessments were treated as negative entries (but see definition of model M1 below which amounts to the last observation carried forward).

To assess the correlation between the candidate risk factors, pairwise-associations between any two (binary) factors were analyzed. Association was determined as the φ-coefficient where one day of hospital stay was considered as one observation. Correlation clusters were identified by $\varphi > 0.3$ (**Appendix Figure 1**). Based on clinical expertise, correlated variables were 1) rejected, 2) merged to an overarching variable, or 3) reformatted to multilevel risk factors. Finally, 26 of the assessed 46 candidate risk factors were included in the regression models (**Appendix Table 1**).

Statistical analysis

Univariable and multivariable Cox proportional hazards models were used to determine the impact of the included 26 exposure variables on nvHAP incidence. The observations were clustered by hospital admission. In the models, time at risk was determined as the period between day 3 of hospital stay until day two after hospital discharge (**Figure 1A**). Days with an invasive respiratory device present and one day thereafter were excluded from the time at risk because pneumonia events occurring in this time would be categorized as VAP (**Figure 1B**). Days after the occurrence of nvHAP and after admission to the ICU were censored, the latter because information on several exposure variables, such as medication data, was not available during

ICU stays. Exposures starting at the day of symptom onset were not considered. Exposures were included as time-updated variables: a constant hazard ratio HR_0 was assumed for calendar days with a positive entry for a given exposure variable. The days after the end of an exposure period were considered in univariable analysis using two approaches: In model U1 (non-decaying HR model), persistent risk after the exposure ends was assumed (β=0) (**Figure 1C**). In model U2 (decaying HR model), we allowed for a linear decrease of the logarithm of the hazard ratio after the end of the exposure period ($\log[HR(t)] = \log[HR_0] - \beta * t$, where t quantifies the decay after the end of the exposure). This corresponds to an exponential decay with rate β of the (unlogged) hazard ratio. The hazard ratio was updated daily, leading to a stair-stepped decay (with step-size of 1 day, see **Figure 1D)**. Multivariable analysis was also performed in two approaches. In model M1, no decay of the HR for all risk factors was assumed. In the main model M2, decay was assumed for those factors which had a lower Bayesian information criterion (BIC) in model U2 compared to BIC in corresponding model U1. For the remaining factors, no decay (i.e., β=0) was assumed. Calculation of confidence intervals of the hazard ratios were based on Wald statistics. To assess the robustness of our analysis, we performed additional sensitivity analyses (S1 to S6), which are described in **Appendix Sensitivity analyses**.

All statistical computations were performed using R (version 4.0.0).(16)

RESULTS

The patient population consisted of 69,616 hospitalizations. After the exclusion of 744 patients with respiratory device present during the entire hospitalization, and 2,871 patients with direct admission to the ICU, the study population included 66,001

hospitalizations in 46,699 patients and 10838 patients had more than one admission. Of all hospitalizations, 314 (0.48%) had non-fungal nvHAP, with 6 patients having more than one episode. A total of 471,401 days were considered as days at risk, including the two days after discharge of a patient, and excluding the first two hospitalization days, the days after nvHAP event, the days with a respiratory device present, and the days on or after an ICU stay.

Median age of in-patient was 57 years (interquartile range [IQR], 38-71), and 32,253 (48.9%) were male. The median duration of hospital stay was 5 days (IQR: 3-9). Median time to nvHAP diagnosis was 9 days (IQR: 5-16). **Table 1** shows the exposures per hospitalization, and per patient days with and without assuming constant exposure after the first occurrence (no decay).

Association of nvHAP with exposures according to uni- and multivariable analysis model M2 is shown in **Figure 2**. Risk factors with strongest independent association with nvHAP were age ≥40, tube feeding, impaired consciousness, and severely impaired activity and mobility. Other variables independently associated with nvHAP were male sex, affiliation to high-risk department (a priori defined as internal medicine and subspecialties, and departments performing cardiac or thoracic surgery), acute dyspnea, swallowing difficulties without tube feeding, tube placement without tube feeding (e.g., tube drainage), opioids, psycholeptics, antineoplastic agents, antibiotics, antimycotics, and general anesthesia. On the other hand, drugs for acid related disorders were not associated with nvHAP, nor was chronic pulmonary disease. Results were largely unchanged when applying Model M1, except that tube placement without tube feeding and general anesthesia lost significance (**Appendix figure 2**). In sensitivity analysis S3, considering exposure relevant at least two, three, and four days before nvHAP, acute dyspnea, general

anesthesia, psycholeptics and antibiotics lost association with nvHAP (**Appendix figures 5a-c**). Sensitivity analysis S4, where decay was assumed only for factors in which it strongly improves the univariable model according to the BIC, general anesthesia lost significance (**Appendix figure 6**). Similar effect sizes were observed in sensitivity analysis S1, S2, S5 and S6 compared to the main model (see **Appendix figures 3-4 and 7-8**).

Table 2 shows the number of days until the association of an exposure with nvHAP fully decays. Significant decay was found for impaired mobility, impaired consciousness, swallowing difficulties, tube placement and tube feeding, pain and opioids, psycholeptics, and general anesthesia. Overall, decay occurred within 3.6 and 13.2 days after exposure had stopped.

DISCUSSION

In this study including more than 60,000 hospitalizations, 470,000 patient days at risk and 314 episodes of non-fungal nvHAP, several independent risk factors for nvHAP were identified. Non-modifiable risk factors were age and male sex. Modifiable or potentially modifiable risk factors with strongest nvHAP association were tube feeding, enteral tube placement without tube feeding, impaired consciousness, severely impaired activity and mobility, and dysphagia. The impact of several risk factors exhibited a rapid decay of association with nvHAP after exposure ended.

Even though nvHAP is one of the most common HAI, little is known about time-varying and thus potentially modifiable risk factors. We found that swallowing difficulties, tube feeding and enteral tubes per se were associated with nvHAP with a hazard ratio of 1.9 or higher. Dysphagic patients are at increased risk for aspiration

pneumonia and the association was yet mainly shown in patients with stroke (17). Our study now shows an association in a very broad patient population. While other authors found nasogastric tubes to increase HAP risk (5, 7, 18), we were able to specify that patients receiving tube feeding are at highest risk, while tubes not used for enteral feeding are associated with nvHAP to a weaker extent. We assume that the latter tubes are mainly placed as draining tubes, as in patients with bowel obstruction, and postulate that these patients are inherently at substantial risk for aspiration pneumonia not because, but despite having draining tubes. Second, in accordance with other studies, impaired consciousness was associated with nvHAP (5, 9, 19). Furthermore, general anesthesia, a procedure associated with unconsciousness, temporal paralysis and suppressed cough reflex was identified as a risk factor for nvHAP. Third, severely impaired mobility defined as “inability or dependency on major support to leave the bed”, seems to be an independent nvHAP risk factor, in accordance with previous studies that identified immobilization and paralysis to increase nvHAP risk (8, 11). Reduced ventilation and clearance of secretions of the lungs, contributing to the development of atelectasis in dependent lung regions might be one pathophysiological explanation.

Like other authors, we found that higher age and male sex are non-modifiable risk factors for nvHAP (10, 11). Contrary to other studies (8, 11), chronic pulmonary disease was not shown to increase nvHAP risk. Instead, we found an association between acute dyspnea and nvHAP. Congestive heart failure, a common cause of dyspnea in the hospital, is a known risk factor for HAP (11, 20). As the association of dyspnea with nvHAP lost significance in the sensitivity analysis considering exposure relevant only two or more days before occurrence of nvHAP, dyspnea might also be an early sign of developing pneumonia.

We found an association of opioids, psycholeptics, antineoplastic agents, antimycotics, or antibiotics and nvHAP. For some medications, a pathophysiological explanation and thus causal effect is probable, like opioids and psycholeptics having a sedative, and antineoplastic agents an immunosuppressive effect. On the other hand, the association of some medications (e.g., antimycotics and antibiotics) and nvHAP is probably a result of residual confounding, as these medications are given – also prophylactically – to severely ill, immunosuppressed patients. Whether proton pump inhibitors increase the risk for (nosocomial) pneumonia is controversial, some studies found an association (10, 21-23), others did not (24, 25). While we found an association of drugs for acid related disorders with nvHAP in the univariable analysis, our results did not show an independent association.

Most of the time-varying risk factors showed a full post-exposure decay of the associated risk within days after the end of exposure. This supports that a patient's risk for pneumonia varies during one hospitalization and suggests that nvHAP is preventable by addressing these risk factors. Oral care interventions are the probably best-researched prevention measure exhibiting a risk reduction of 39% in a meta-analysis of randomized controlled trials (26, 27), and might be especially important in patients with aspiration risk like dysphagic or unconscious patients. Also, small studies investigating mobilization interventions or dysphagia programs have shown a beneficial effect on nvHAP rates (28-30), patients with impaired mobility and swallowing difficulties could be a target population. Drugs like opioids or sedatives could be dosed cautiously or even been withheld to prevent overdosing with somnolence and shallow breathing. In patients needing enteral feeding, strict elevation of head of bed should be applied to prevent aspiration (31),. In recent years, several authors found prevention bundles against nvHAP or postoperative pneumonia to effectively lower pneumonia rates by 40-80% (33-35). These bundles

among other measures included mobilization, respiratory therapy, and/or head of bed elevation besides oral care interventions.

Our study is unique for assessing a combination of time-varying exposures including data from daily nursing assessments, allowing inclusion of the patient's changing medical condition and their signs and symptoms into the risk factor analysis. Still, the study has some limitations. First, as a single center study it is not necessarily generalizable to other patient populations. The included population is broad, and specific patient populations might exhibit specific risk factors not identified in this study. Second, as medication and other data was not accessible in the ICU medical record, we excluded all patient days during and after ICU stay, prohibiting assessment of some specific potentially interesting exposures like 'post-intubation'. Third, we did not account for the competing risk of death and we treated missing entries as negative. Fourth, data of first and last days of stay were incomplete. However, we addressed this limitation by performing a sensitivity analyses, which have shown robust effects.

In conclusion, this study identified key risk factors of nvHAP. By allowing for a dynamic effect in the analysis, we provide strong evidence that nvHAP risk changes during the hospital stay. Some of the time-varying factors displayed a decay after the exposure, such as enteral feeding, impaired consciousness, impaired mobility, and swallowing difficulties. Many of these factors represent potential targets for prevention measures. Of course, there is substantial uncertainty on the effect of prevention interventions targeting these risk factors, as risk factors often co-occur, and causal relationship with nvHAP and modifiability might only be given in a subset of patients. Additionally, potential side effects of prevention measures, like falls in mobilization, have to be carefully considered. Even though attributable efficacy

cannot be predicted, further research aiming to establish most effective prevention bundles could be based on the findings of this study.

Contributions

AW, VNK, SPK, HS and RDK designed the study. AW and WJ acquired the data, and VNK, SB and RDK performed statistical analysis. AW, VNK, SPK, PWS, HS and RDK analyzed and interpreted the data. AW and VNK drafted the manuscript, and SPK, SB, PWS, WJ, HS, and RDK provided critical review of the manuscript for important intellectual content. All authors agree with the content and conclusions of this manuscript.

Acknowledgement

Preliminary results of this manuscript were accepted as poster presentation at ECCMID 2020 (congress was cancelled due to COVID-19 pandemic), and were presented at the Joint Annual Meeting Swiss Society of Hospital Epidemiology 2020 and at ECCMID 2021.

Conflicts of interest

None to declare for all authors

Funding

AW and PWS were supported by the academic career program “Filling the gap” of the Medical Faculty of the University of Zurich.

This project was supported from the “Innovationspool”, a University Hospital Zurich funding program for developing new approaches in medical diagnostics and treatment.

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Figure 1 Definitions

Caption: A) Scheme of the days considered as time at risk; B) Time excluded due to respiratory device present; C and D) Functional dependence of the Hazard ratio.

Figure 2 Uni- and multivariable Cox Proportional Hazards model (U2 and M2) with hazard ratios for exposure and hazard ratios for decay of exposure

Caption: Decay is shown for factors in which it improves the univariable model according to the Bayesian information criterion (BIC)

Abbreviations: ATC, Anatomical Therapeutic Chemical Classification System; BMI, body mass index; ERCP, endoscopic retrograde cholangio-pancreatography

Table 1 Hospitalizations and patient days exposed to candidate risk factors

Name	Number of exposed hospitalizations (n=66'001)	Number of exposed patient days (n= 471'401)	Number of exposed patient days, assuming constant exposure after first occurrence (no decay) (n= 471'401)
Patient characteristics			
Age (≥ 40, <60)	18'095 (27.4%)	123'377 (26.2%)	123'377 (26.2%)
Age ≥ 60	30'332 (46.0%)	241'763 (51.3%)	241'763 (51.3%)
Male Sex	32'253 (48.9%)	231'142 (49.0%)	231'142 (49.0%)
High BMI	25'817 (39.1%)	191'259 (40.6%)	191'259 (40.6%)
Affiliation			
Affiliation to high risk department	26'371 (40.0%)	184'582 (39.2%)	224'976 (47.7%)
Symptoms and medical conditions			
Severely impaired activity and mobility	17'182 (26.0%)	68'445 (14.5%)	163'670 (34.7%)
Abdominal or thoracic injuries or surgeries	9'800 (14.8%)	54'592 (11.6%)	75'447 (16.0%)
Acute dyspnea	8'360 (12.7%)	46'474 (9.9%)	79'909 (17.0%)
Impaired consciousness	7'623 (11.5%)	17'012 (3.6%)	67'902 (14.4%)
Chronic pulmonary disease	6'169 (9.3%)	40'088 (8.5%)	53'624 (11.4%)
Nausea	7'554 (11.4%)	26'575 (5.6%)	72'490 (15.4%)
Medical conditions +/- interventions (multilevel exposures)			
Swallowing difficulty but no tube feeding	1'838 (2.8%)	8'598 (1.8%)	14'990 (3.2%)
Tube placement but no tube feeding	1'741 (2.6%)	5'467 (1.2%)	13'922 (3.0%)
Tube feeding	1'211 (1.8%)	9'964 (2.1%)	13'700 (2.9%)
Non-opioid analgetics but no moderate/severe pain and no opioids	26'619 (40.3%)	64'966 (13.8%)	133'304 (28.3%)
Moderate/severe or chronic pain but no opioids	10'265 (15.6%)	40'739 (8.6%)	60'823 (12.9%)
Opioids	20'565 (31.2%)	141'171 (29.9%)	178'681 (37.9%)
Medication			
Drugs for Acid related disorders (ATC A02)	31'928 (48.4%)	207'304 (44.0%)	261'335 (55.4%)
Psycholeptics (ATC N05)	29'927 (45.3%)	108'332 (23.0%)	233'379 (49.5%)
Antineoplastic agents (ATC L01)	3'000 (4.5%)	10'803 (2.3%)	31'001 (6.6%)
Immunosuppressants (ATC L04)	3'181 (4.8%)	23'995 (5.1%)	29'113 (6.2%)
Antibiotics (ATC J01)	24'254 (36.7%)	145'346 (30.8%)	217'160 (46.1%)
Antimycotics (ATC J02)	2'196 (3.3%)	14'560 (3.1%)	26'589 (5.6%)
Procedures			
Gastroscopy or ERCP	2'180 (3.3%)	2255 (0.5%)	19'152 (4.1%)
General anaesthesia	27'505 (41.7%)	22'056 (4.7%)	167'712 (35.6%)
Analgosedation	2'881 (4.4%)	1870 (0.4%)	19'598 (4.2%)

Caption: Prevalence is given as a number of hospitalizations exposed to the factor at least once, the number of days in which the patients were exposed, and the number of patient days the patient was exposed assuming constant exposure after first occurrence of the factor.
Abbreviations: ATC, Anatomical Therapeutic Chemical Classification System; BMI, body mass index; DOS, Delirium observation scale; ERCP, Endoscopic retrograde cholangio-pancreatography

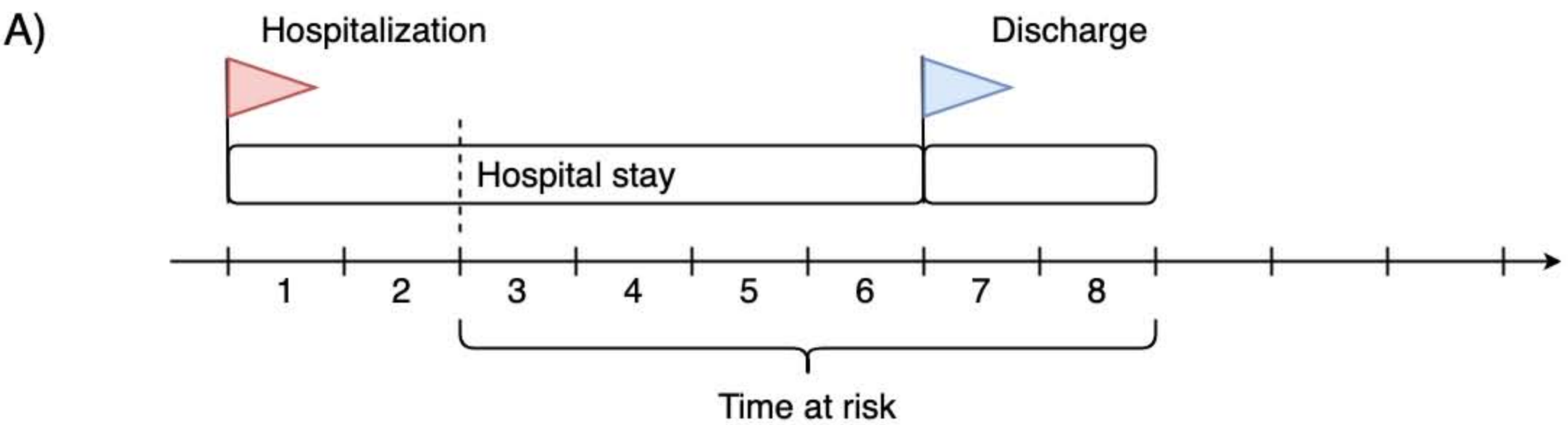
Table 2 Decay of association after end of exposure

Name of the exposure	Beta (decay slope, see Figure 1 D)	Decay in days for variables with significant Beta (univariable analysis)
Affiliation to high risk department	-0.07 (-0.21,0.07)	
Severely impaired activity and mobility*	-0.20 (-0.32,-0.09)	7.1
Abdominal or thoracic injuries or surgeries*	0.03 (-0.02,0.07)	
Acute dyspnea*	-0.07 (-0.16,0.01)	
Impaired consciousness	-0.17 (-0.25,-0.08)	11.2
Chronic pulmonary disease*	-0.06 (-0.18,0.06)	
Swallowing difficulty but no tube feeding	-0.14 (-0.26,-0.03)	10.5
Tube placement but no tube feeding		9.8
Tube feeding		13.2
Non-opioid analgetics but no moderate/severe pain and no opioids	-0.16 (-0.26,-0.05)	3.7
Moderate/severe or chronic pain but no opioids		3.6
Opioids		6.1
Nausea*	0 (-0.04,0.04)	
Drugs for Acid related disorders (ATC A02)	-0.22 (-0.48,0.04)	
Psycholeptics (ATC N05)	-0.13 (-0.21,-0.05)	6.5
Antineoplastic agents (ATC L01)	-0.01 (-0.04,0.03)	
Immunosuppressants (ATC L04)	-0.6 (-1.59,0.4)	
Antibiotics (ATC J01)	-0.02 (-0.07,0.02)	
Antimycotics (ATC J02)	-0.05 (-0.09,0)	
Gastroscopy or ERCP	0 (-0.04,0.04)	
General anaesthesia	-0.08 (-0.15,-0.01)	4.6
Analgosedation	0.01 (-0.06,0.08)	

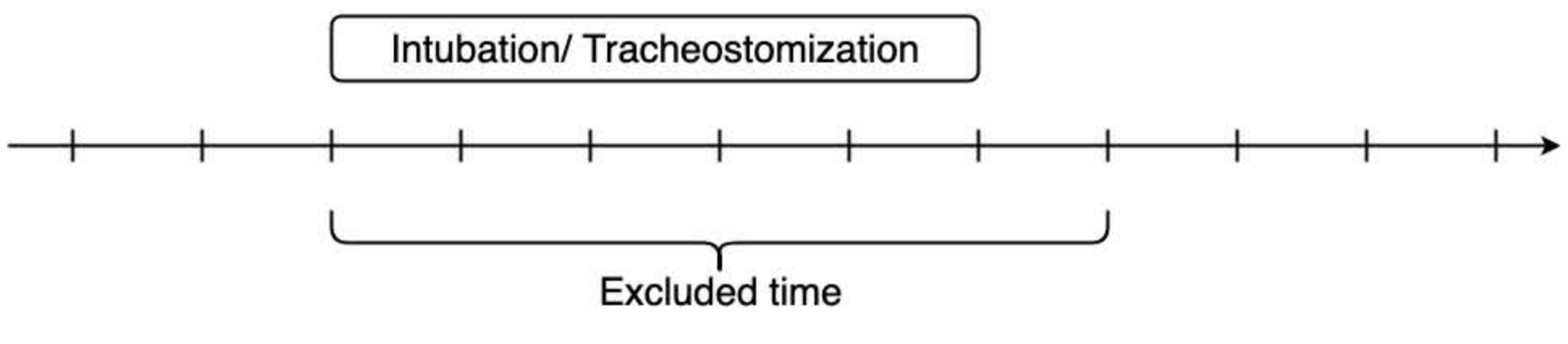
Caption: Results of the analysis utilizing univariable proportional-hazards models, showing number of days until full decay for variables with significant Beta.

Abbreviations: ATC, Anatomical Therapeutic Chemical Classification System; ERCP, Endoscopic retrograde cholangio-pancreatography

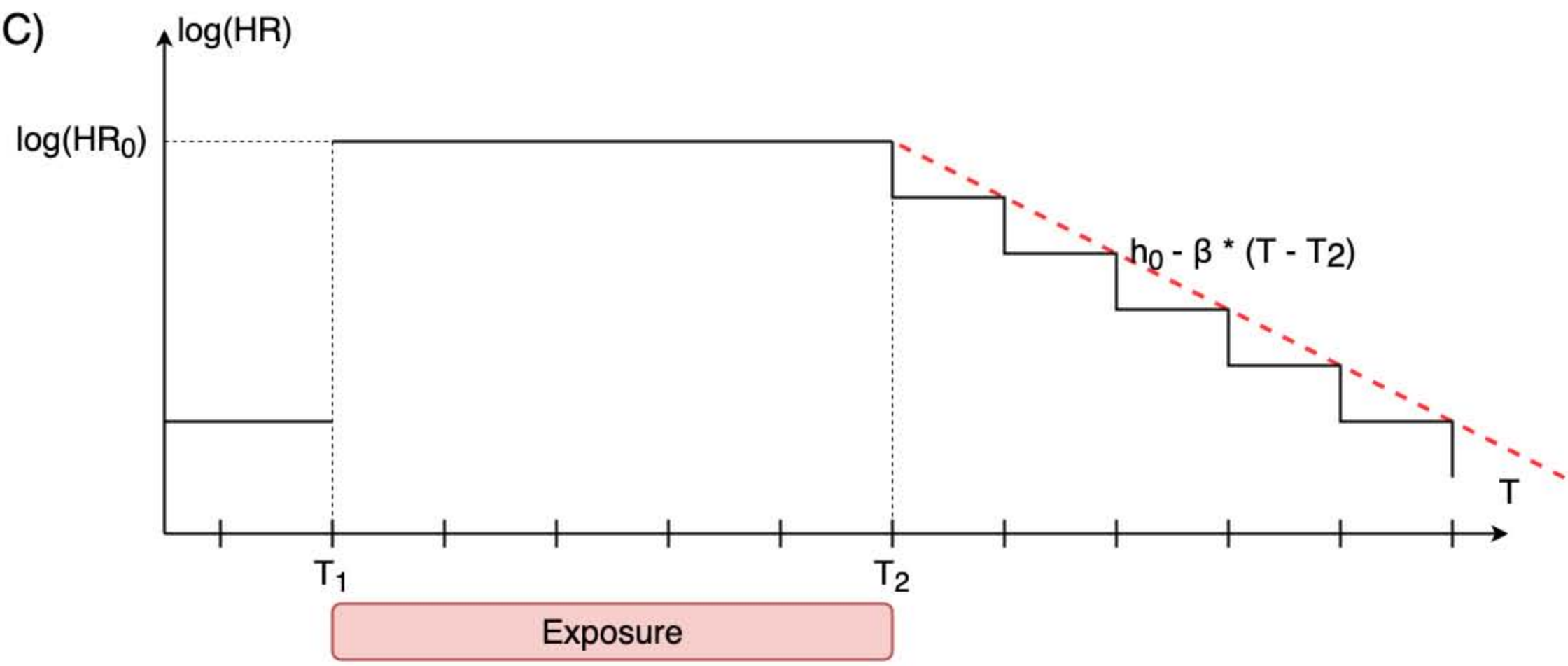
A)


Hospitalization
Discharge
Hospital stay
1
2
3
4
5
6
7
8
Time at risk

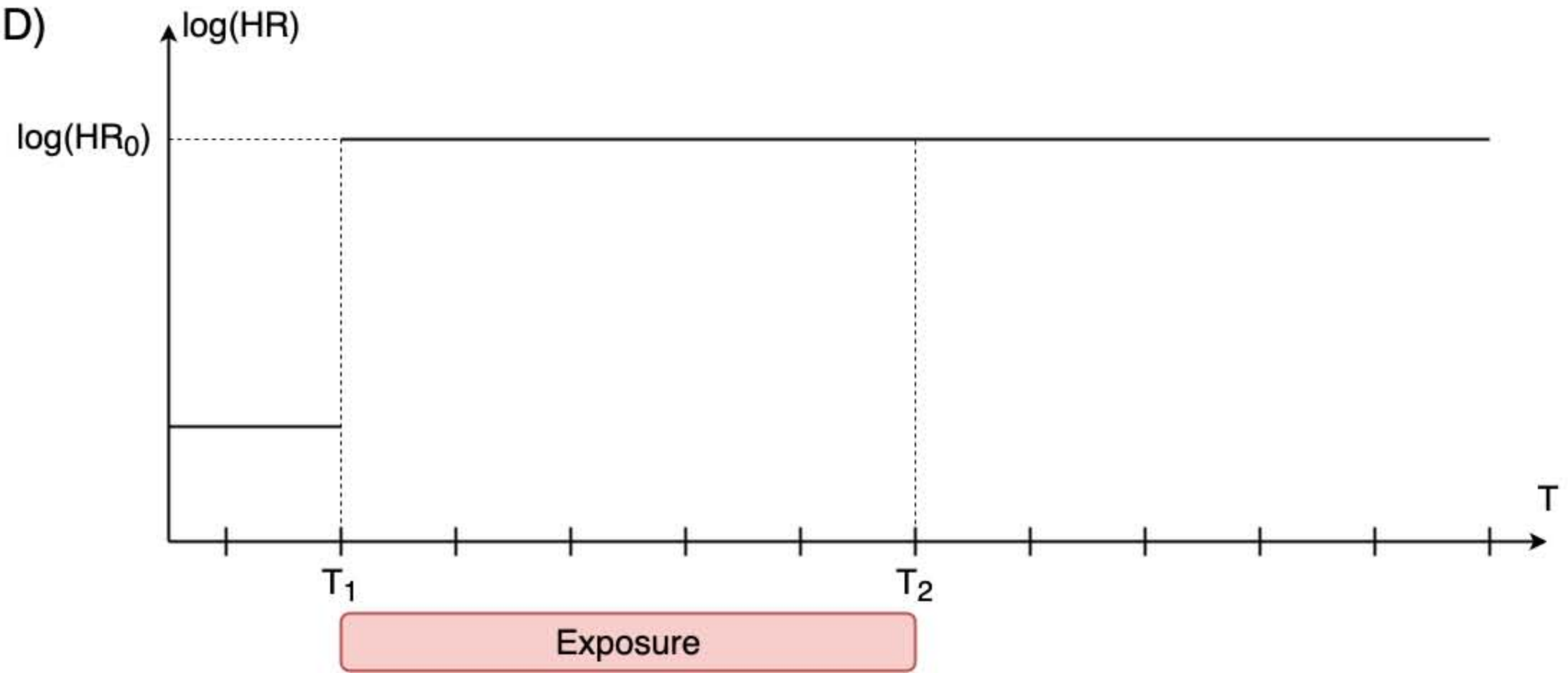
B)

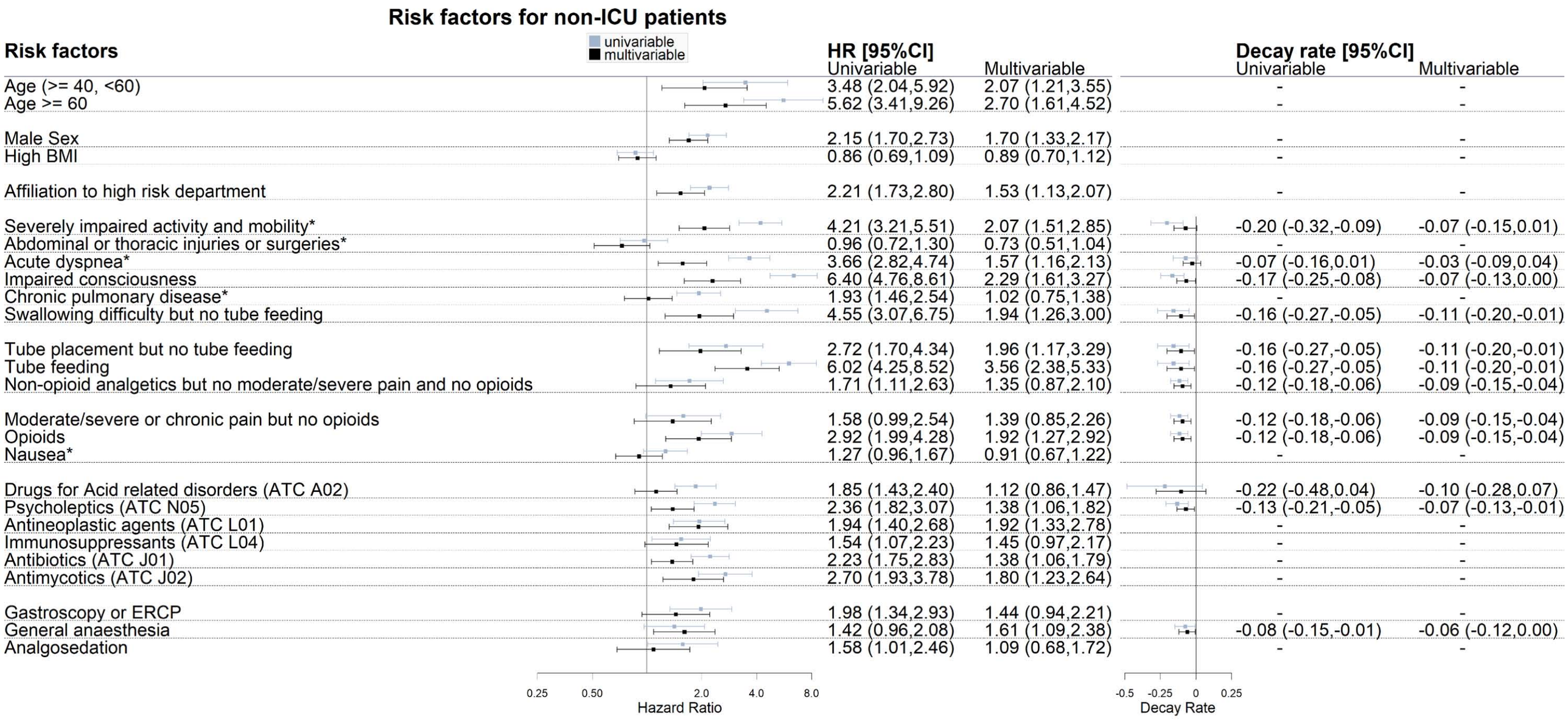

Intubation/ Tracheostomization
Excluded time

C)


log(HR)
log(HR0)
h0 - β * (T - T2)
T
T1
T2
Exposure

D)


log(HR)
log(HR0)
T
T1
T2
Exposure


Risk factors for non-ICU patients
univariable
multivariable
Risk factors
HR [95%CI]
Univariable
Multivariable
Decay rate [95%CI]
Univariable
Multivariable
Age (>= 40, <60) 3.48 (2.04,5.92) 2.07 (1.21,3.55) - -
Age >= 60 5.62 (3.41,9.26) 2.70 (1.61,4.52) - -
Male Sex 2.15 (1.70,2.73) 1.70 (1.33,2.17) - -
High BMI 0.86 (0.69,1.09) 0.89 (0.70,1.12) - -
Affiliation to high risk department 2.21 (1.73,2.80) 1.53 (1.13,2.07) - -
Severely impaired activity and mobility* 4.21 (3.21,5.51) 2.07 (1.51,2.85) -0.20 (-0.32,-0.09) -0.07 (-0.15,0.01)
Abdominal or thoracic injuries or surgeries* 0.96 (0.72,1.30) 0.73 (0.51,1.04) - -
Acute dyspnea* 3.66 (2.82,4.74) 1.57 (1.16,2.13) -0.07 (-0.16,0.01) -0.03 (-0.09,0.04)
Impaired consciousness 6.40 (4.76,8.61) 2.29 (1.61,3.27) -0.17 (-0.25,-0.08) -0.07 (-0.13,0.00)
Chronic pulmonary disease* 1.93 (1.46,2.54) 1.02 (0.75,1.38) - -
Swallowing difficulty but no tube feeding 4.55 (3.07,6.75) 1.94 (1.26,3.00) -0.16 (-0.27,-0.05) -0.11 (-0.20,-0.01)
Tube placement but no tube feeding 2.72 (1.70,4.34) 1.96 (1.17,3.29) -0.16 (-0.27,-0.05) -0.11 (-0.20,-0.01)
Tube feeding 6.02 (4.25,8.52) 3.56 (2.38,5.33) -0.16 (-0.27,-0.05) -0.11 (-0.20,-0.01)
Non-opioid analgetics but no moderate/severe pain and no opioids 1.71 (1.11,2.63) 1.35 (0.87,2.10) -0.12 (-0.18,-0.06) -0.09 (-0.15,-0.04)
Moderate/severe or chronic pain but no opioids 1.58 (0.99,2.54) 1.39 (0.85,2.26) -0.12 (-0.18,-0.06) -0.09 (-0.15,-0.04)
Opioids 2.92 (1.99,4.28) 1.92 (1.27,2.92) -0.12 (-0.18,-0.06) -0.09 (-0.15,-0.04)
Nausea* 1.27 (0.96,1.67) 0.91 (0.67,1.22) - -
Drugs for Acid related disorders (ATC A02) 1.85 (1.43,2.40) 1.12 (0.86,1.47) -0.22 (-0.48,0.04) -0.10 (-0.28,0.07)
Psycholeptics (ATC N05) 2.36 (1.82,3.07) 1.38 (1.06,1.82) -0.13 (-0.21,-0.05) -0.07 (-0.13,-0.01)
Antineoplastic agents (ATC L01) 1.94 (1.40,2.68) 1.92 (1.33,2.78) - -
Immunosuppressants (ATC L04) 1.54 (1.07,2.23) 1.45 (0.97,2.17) - -
Antibiotics (ATC J01) 2.23 (1.75,2.83) 1.38 (1.06,1.79) - -
Antimycotics (ATC J02) 2.70 (1.93,3.78) 1.80 (1.23,2.64) - -
Gastroscopy or ERCP 1.98 (1.34,2.93) 1.44 (0.94,2.21) - -
General anaesthesia 1.42 (0.96,2.08) 1.61 (1.09,2.38) -0.08 (-0.15,-0.01) -0.06 (-0.12,0.00)
Analgosedation 1.58 (1.01,2.46) 1.09 (0.68,1.72) - -
0.25
0.50
2.0
4.0
8.0
Hazard Ratio
-0.5
-0.25
0
0.25
Decay Rate