Analysis protocol

Title: Risk of Self-harm following Discharge from an Acute Somatic Hospitalization

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Background

A well-designed discharge process following somatic hospitalization involves several key elements to ensure the continuity of care and minimize the risk of adverse events. The discharge process could be influenced by strained hospital resources, potentially leading to expedited discharge, limited access to post-discharge support services, and increased reliance on primary health care, which may impact the continuity and quality of patient care.[1-3] However, the extent to which the discharge process also addresses the immediate mental health state and needs of patients remains unclear. It is well known that individuals recently discharged from a psychiatric hospital face a substantially increased risk of suicide.[4,5] While several additional studies have highlighted an elevated risk of suicide in individuals with acute somatic conditions, such as e.g. cardiovascular diseases,[6-10] our understanding of the post-discharge phase as a potential vulnerable period remains relatively limited.

This paper aims to comprehensively assess associations between timing of discharge following an acute somatic hospitalization and the risk of death or hospitalization for deliberate self-harm events, covering both fatal and non-fatal cases. In addition, we will assess risk for other accidental events such as intoxications, transport accidents, accidents with undetermined cause and acute contacts and hospitalization in mental health services.

There are several reasons why the post-discharge period may be a vulnerable period. Firstly, somatic diseases can themself trigger mood disorders in diseases that involve inflammatory pathophysiologic mechanisms, such as cancer[11] or cardiovascular diseases.[6-10] Inflammation has also been associated with the emergence of mood disorders.[12] Patients may also experience fluctuating emotional states after an acute somatic episode if they are faced with a poor prognosis and/or have experienced a rapid loss of function. Additionally, the availability of potentially lethal medications, frequently prescribed upon discharge, might elevate the risk of self-harm. This is because having access to lethal means is a widely recognized contributing factor to suicide risk.[13] Medication used for somatic conditions, such as steroids, cardiovascular disease drugs, and chemotherapy/immune modulating therapies, may also have side effects that impact mental health and suicidality.

Assessing the causal mechanism behind a potential increased risk after discharge can be challenging. There are several factors indicating a higher vulnerability immediately following discharge, which may not be directly associated with the discharge itself. However, since avoiding hospital discharges is not feasible, it is important to evaluate any potential heightened risk during a period when preventive measures can be implemented. Given that individuals at greater risk of self-harm are more likely to experience acute hospitalization, we will also examine changes in individual risk following discharge using a self-control design. In this design, we compare an individual's probability of discharge during the period when the outcome of interest occurs with their probability of discharge in previous periods of their life.

Methods

Data

We will utilize data from the whole Norwegian population linked to the Norwegian Patient Registry and the Norwegian Cause of Death Registry, and the Norwegian Municipal Patient Registry. We have access to data from the Norwegian Patient Registry including information on acute hospital admissions occurring between January 1, 2008 and December 31, 2021. Our study uses hospital admissions defined by criteria outlined in Hassani et al.,[14] such that each hospitalization encompasses the patient's hospital entry, transfers within or between hospitals, and concludes upon the patient's discharge. Throughout the study period, each patient is assigned a unique and anonymous identification number, enabling us to connect patient information across multiple registries. Data on cause-specific mortality is readily available from the Norwegian Cause of Death Registry.

Outcome

The main outcome is deliberate self-harm events. Outcome ascertainment will be measured using diagnoses in the International Statistical Classification of Diseases and Related Health Problems (ICD-10),[15] registered after acute contact with specialised health services or as cause of death. Self-harm is indicated by codes X60-84 (suicide) and X6n (intentional self-harm).

Secondary outcomes include intoxications (indicated by ICD-10 codes T4n-T50, T51-T60, T65, F10-19 and (only code F1x.0)), transport accidents (indicated by ICD-10 codes V01-V99), accidents with undetermined cause (indicated by ICD-10 codes Y10-Y34) and any contacts with mental health services.

Exposure

An individual in the study will be considered exposed in the period after discharge from an acute hospital episode. The post discharge periods will be measured with different time periods after discharge. To strike a balance between sufficient statistical power and capturing the potentially most stressful time period, we will select specific time windows for our analysis. It is crucial to emphasize that this selection will also consider the low incidence of suicide, guaranteeing that we capture meaningful number of events within relevant time intervals.

Sub-groups

We anticipate that certain acute diseases may carry a higher risk compared to others, and we will analyse these events separately. To achieve this, we will perform analyses for each chapter of main diagnoses in the ICD-10 based on organ systems. Additionally, we will conduct analyses for specific main diagnoses that are associated with a poor prognosis and/or significant functional loss. These diagnoses include cerebrovascular diseases, myocardial infarction, heart failure, chronic lower respiratory diseases, traumatic amputation of upper or lower extremities, and severe burns involving more than 10% of the body surface area. Furthermore, we will consider medical conditions known to be associated with significant pain. These conditions encompass kidney stones, acute myocardial infarction, acute abdominal conditions (such as appendicitis, pancreatitis, and ulcers), gynaecological conditions (such as endometriosis and ectopic pregnancy), traumas, postoperative pain following major surgeries, and pain resulting from infections or pathogen-related conditions like shingles. Chronic or recurring pain conditions such as neuropathies/neuralgia, cancer-related pain, sciatica, gout, arthritis, migraines, and other types of headaches will also be included. We will also examine the discharge of hospitalization with specific diagnoses related to infections/inflammation, such as pneumonia, urinary tract infections, meningitis, influenza, COVID-19, and rheumatoid arthritis.

Considering the potential impact of staffing levels, we will assess the effects of discharges on weekends, holidays, and days preceding weekends and holidays, which may carry an increased risk.

We will also analyse the effects separately according to hospital type, as well as individuals with a history of mental illness. To explore potential gender differences, separate analyses will be conducted for men and women. Moreover, we will perform separate analyses for individuals with different educational backgrounds, categorizing them as high, medium, and low. Finally, age-specific analyses will be conducted for individuals aged 12-20, 21-64, and >64 years.

Study design and statistical analyses

The follow-up will be between July 1, 2008, and December 31, 2021. We will follow all individuals >12 years of age due to the rarity of the outcomes before that age. Individuals will be followed until outcome, the start of a new acute hospitalization episode, death from any cause, emigration, or the end of the follow-up period (December 31, 2021), whichever happened first. To address the potential impact of multiple consecutive acute hospitalizations, we will implement a truncation procedure that excludes information from subsequent discharges occurring within 180 days of the previous discharge. This approach ensures that we focus on distinct episodes of hospitalization and avoid the cumulative effects of multiple acute hospitalizations in a sequence. We will analyse time dependent risk in two ways: Cox regression and case-crossover.

Cox regression

Cox regression will be used to estimate hazard ratios of a given outcome following a potential discharge from an acute hospitalization. The time following discharge from an acute hospitalization will be a time-varying covariate, initially designated as 0 until a discharge occurs (if it does), and then changed to 1 after the discharge for a given time window. We will use age as the time axis.

Case-crossover

We will also employ a case-crossover design[16] to examine the association between post-discharge from an acute hospital episode and subsequent risk change. The case-crossover design is a self-matching approach that compares exposure levels during a defined risk period preceding the outcome event (case period) with exposure levels during control periods in the same individual at different time points (reference periods). This design inherently accounts for individual-level time-invariant confounders. We establish our case-crossover design by incorporating data from all previously observed periods leading up to the case period. The design assumes a constant risk of exposure, treating the person-time during the case period as exchangeable with the same individual's person-time during control periods. From the target population of all somatic discharges, we will select case-crossover samples for each outcome of interest. Each sample consists of patients who were exposed to at least one acute somatic discharge and experience one of the outcomes. By adopting a discrete-time perspective, we consider each day as an independent unit for analysis. We exclude the first 30 days preceding the case period to avoid carry over effects.

The case-crossover design is susceptible to exposure trends due to the event being confined to the end of the follow-up period.[17] To mitigate this concern, we will adopt a case-case-time-control approach proposed by Wang et al.[18] This approach entails conducting crossover analyses within cases and utilizing information from future-case controls. By limiting controls to future cases, we can enhance matching and effectively address potential exposure trends. This approach allows for adjustment of exposure trends due to seasonal variations and aging, which would further improve the validity of the analysis.

In this approach, we reverse the roles of the dependent and independent variables when estimating the conditional logistic regression model. This reversal is possible due to the symmetric properties of the odds ratio. As a result, we will analyse the risk of exposure during specific periods in relation to whether the outcome occurred or not. By incorporating exposure information from future cases, we avoid the issue of perfect correlation with time. To assess the association between post-discharge

periods and outcomes, we will calculate the odds of being in a specific post-discharge period during the case period, compared to being in the same discharge state during control periods occurring before the outcome (control periods). We will use odds ratios along with 95% confidence intervals. This estimation will be performed through a conditional logistic regression as a fixed effect estimator.

Power considerations for a case-crossover analysis

A preliminary investigation of available data shows that there were 7 453 suicides from 2008 to 2021. Among these, 194, 329, 430 and 516 occurred within 1, 2, 3 and 4 weeks after a discharge from an acute, somatic hospital stay. To find an approximate risk of exposure during time-windows of different lengths, needed to assess statistical power, we consider the two years preceding the suicide. In this time interval there was approximately one percent probability of being in within one week of a discharge from an acute, somatic hospital stay. Table 1 shows calculations from Dupont's sample size formula[19,20] approximating the needed cases for relevant parameters. If we assume, roughly, that the probability of exposure is between 0.01 for a one-week time window to 0.04 for a four-week time window. The data for this study should be able to detect associations with OR>3 with probability 80% when we use case and reference period lengths of 1 week, but weaker associations require that we use periods of two or more weeks. Including self-harm events that do not lead to death will provide more statistical power.

			Required number of cases when using M reference periods			
Length of time period	**P(exposure)**	**Effect size (OR)**	**M=1**	**M=2**	**M=3**	**M=4**
1 week	0.01	2	1220	900	840	830
1 week	0.01	3	600	360	290	250
1 week	0.01	4	450	250	180	140
2 weeks	0.02	2	610	450	410	410
2 weeks	0.02	3	300	180	140	120
2 weeks	0.02	4	220	120	90	70
3 weeks	0.03	2	400	300	270	270
3 weeks	0.03	3	200	120	90	80
3 weeks	0.03	4	150	80	60	40
4 weeks	0.04	2	300	220	200	200
4 weeks	0.04	3	150	90	70	60
4 weeks	0.04	4	110	60	40	30

Table 1: Number of cases needed to detect an association with 80 percent probability with alpha-level 0.05 and various effect sizes numbers of control periods, and exposure probabilities corresponding roughly to one to four weeks risk periods. Case numbers that are likely achievable with available data on suicides are highlighted in green.

Ethical approval and transparency

The Regional Committees for Medical and Health Research Ethics has approved the study, 2016/2159/REK Midt. All codes for preparation and analysis of the data will be made available on Github.

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