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Risk of suicide attempts and self-harm after 1.4 million general medical hospitalizations of men with mental illness

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ABSTRACT

Background: The short-term risk of suicide after medical hospital discharge is four times higher among men compared with women. As previous work has identified female-specific antecedents of suicide-related behavior after medical hospitalization of women with serious mental illness, we examined predictors among a similar population of men with multimorbidity.

Methods: Classification and regression tree (CART) models were developed and validated using electronic health records (EHRs) from 1,423,161 medical (non-psychiatric) hospitalizations of men $\geq$ 18-years-old with an existing diagnosis of a depressive disorder, bipolar disorder, or chronic psychosis. Hospitalizations occurred between 2009 and 2017. Risk groups were evaluated using an independent testing set. The primary outcome was readmission within one year associated with ICD-9 or -10 code for self-harm or attempt.

Results: The 1-year readmission rate for intentional self-harm and suicide attempt was 3.9% (55,337/1,423,161 hospitalizations). The classification model discriminated risk with area under the curve (AUC) 0.73 (Confidence Interval [95%CI] 0.68–0.74), accuracy 0.82 (95%CI 0.71–0.83), sensitivity 82.6% (95%CI 81.2–84), and specificity 83.1% (95%CI 81.7–84.5). Strongest predictors were medical comorbidity, prior self-harm, age, and prior hospitalization. Men with greater medical comorbidity burden and prior self-harm were at highest risk (Odds Ratio [OR] 3.10, 95%CI 3.02–3.18), as were men $<$ 62-years-old with few medical comorbidities (OR 1.11 95% CI 1.08–1.13).

Limitations: The study focused on medical hospitalizations for suicide attempt and thus captured only severe attempts resulting in hospitalization.

Conclusions: After medical hospitalization, men with serious mental illness experienced a high risk of self-harm (1:25 hospitalizations). Risk was particularly elevated among younger patients without prior medical conditions and older patients with medical comorbidity and prior self-harm.

1. Introduction

Men die by suicide at more than twice the rate of women worldwide, with 6.3 deaths per 100,000 women and 13.9 deaths per 100,000 men (Ritchie et al., 2015). In the United States, the suicide rate for males is 3.5–4.5 times that for females (Hedegaard et al., 2020). Sex differences in suicide, suicide attempts, and non-fatal intentional self-harm behaviors are well-established (Dombrovski et al., 2008; Schrijvers et al., 2012). Men and women also differ in the antecedents of these behaviors (Oquendo et al., 2007). Knowledge of sex-specific risk factors in highly vulnerable populations (Montgomery et al., 2021) may clarify mechanisms of risk for self-harm and further the precision of suicide prevention efforts (Edgcomb et al., 2021).

Sex differences in self-harm behavior after hospitalization are pronounced (Jiang et al., 2021) and maybe even more notable after medical compared with psychiatric hospitalization (Olfson et al., 2016). For example, the 90-day rate of suicide is approximately four times as high for men as for women following medical hospitalizations (Olfson et al.,

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2016). However, sex-specific risk factors of self-harm following medical illness are not well-understood. A Danish registry study found that illnesses in most organs or systems increased post-discharge suicide risk in women, whereas neoplasms increased risk significantly more in men (Qin et al., 2013). Another recent registry-based study suggested that physical health diagnoses contributed more to suicide prediction for men than for women (Gradus et al., 2020).

Self-harm following medical hospitalization is challenging to predict and prevent partly because of the protean interactions between mental disorders and other health conditions. Mental illness and physical illness independently increase the risk of lifetime self-harm (Barak-Corren et al., 2017; Stene-Larsen and Reneflot, 2019), and the co-occurrence of major mental disorders and other health conditions is strikingly common (Prince et al., 2007). However, efforts to describe antecedents of self-harm among people with recent medical illnesses and underlying major psychiatric illnesses are scarce (Edgcomb et al., 2020; Hawkins et al., 2016) and often focused on specific disease conditions (Hawkins et al., 2016; Christensen et al., 2007).

Despite the established literature on the compounding risks of male sex (Bilsker and White, 2011), serious mental illness (Hor and Taylor, 2010), and medical hospitalization (Kleespies et al., 2009), and evidence that these three risk factors commonly co-occur (Riblet et al., 2017; Miller et al., 2006), antecedents of self-harm among males with medical and psychiatric comorbidity are not yet well understood. A retrospective cohort study using medical records across two U.S. urban areas (Edgcomb et al., 2021) discovered that women with serious mental illness experience female-specific predictors of self-harm after medical hospitalization (prior pregnancy-related mental illness). However, the study focused exclusively on females and did not evaluate antecedents of self-harm among males.

To address this gap in knowledge, in the present study, we leverage data source described in Edgcomb et al. (2021) and newly focus on adult men with major mood and psychotic disorders, examining antecedents of suicide attempts and intentional self-harm in the year after medical hospital discharge. The primary aim was to develop and validate a model predicting self-harm after medical hospitalization among adult men with comorbid serious mental illness. This study extends previous research by (1) using a large, longitudinal, multi-site sample of men with serious mental illness and recent medical hospitalization, (2) using routinely collected large-scale structured electronic health record (EHR) data, (3) incorporating class imbalance to address limitations of rare outcome modeling, and (4) validating risk groups in an unrelated sample from a different health system, case mix, and geographic region. In keeping with current epidemiologic literature, we anticipated that men with a history of self-harm and pre-existing medical and psychiatric comorbidity would be at greatest risk of self-harm after medical hospitalization.

2. Methods

2.1. Design

This population-based longitudinal cohort study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement guidelines. A machine learning-based classification model was developed using data from the Patient-Centered Outcomes Research Institute (PCORI)-funded INSIGHT Clinical Research Network (INSIGHT-CRN) (Forrest et al., 2021) and the out-of-fold model prediction was used to assess model performance. The model was then applied to a separate dataset (the LA-xDR repository, described below) to validate risk groups across sites.

2.2. Sample

The primary data source (derivation set) was INSIGHT-CRN. This network contains outpatient and inpatient EHR data collected from 2009 through 2017 from seven academic health systems across the New York City (NYC) metropolitan area and includes data on approximately 12 million unique patients. The second data source (validation set) was the LA-xDR repository, containing inpatient and outpatient EHR data on approximately 600,000 unique patients per year from 2006 through 2016 from two large urban medical hospitals in Los Angeles and affiliated outpatient clinics. Both data sources have been previously described elsewhere (Edgcomb et al., 2021). The flowchart for study inclusion criteria is presented in Supplemental Fig. 1. The derivation dataset contained information on 1,415,947 hospitalizations of men meeting inclusion criteria ($N_{patients} = 116{,}762$) and the validation set included 7,214 hospitalizations ($N_{patients} = 1{,}461$).

The initial (index) hospitalization was defined as the first medical hospitalization during the study period. Thus, index hospitalizations were restricted to hospitalizations in medical and surgical units, of (1) adult men (≥18 years old with natal sex male), (2) with a discharge diagnosis of depression (ICD-9 codes 296.20–296.36, 300.4, 309.0, 309.28, 311; ICD-10 codes F32-33.x), bipolar disorder (ICD-9 codes 296.00–296.06, 296.40–296.89, 301.13; ICD-10 codes F31.0–31.9), or schizophrenia or schizoaffective disorder (ICD-9 codes 295.xx; ICD-10 codes F20.x, F25.x) and (3) with record of ≥ 2 hospitalizations during the study period (January 1, 2010–December 31, 2017 for INSIGHT-CRN; January 1, 2007–December 31, 2016 for LA-xDR). Natal sex was used to identify men as information on patient gender identity was insufficiently reported. Index hospitalizations were restricted to those occurring at least 1 year from the first date of data collection (January 1, 2009, for INSIGHT-CRN and January 1, 2006 for LA-xDR) to allow for the capture of pre-hospital care. Transfers within the health system (such as between medical and surgical floors) on continuous days were considered a single hospitalization. Patients discharged with planned readmission were excluded. Only recurrent hospital utilizers were examined (at least two medical hospitalizations during the study) to reduce right censoring common in open system EHR data and control for confounding of readmission predictors with self-harm predictors.

2.3. Predictors

Predictors included sociodemographic data, medications, and healthcare utilization in the year prior to index hospitalization along with associated diagnostic codes. The full list of predictors is provided in Suppl. Table 1. Sociodemographic predictors were natal sex, race/ethnicity, and age at index hospitalization. Medications were classified using RxNorm. Healthcare service utilization included the frequency of emergency department, inpatient, and outpatient encounters in the year prior to index hospitalization.

Diagnoses were determined by ICD-9 and -10 codes and classified using the Elixhauser classification system (Elixhauser et al., 1998), a standardized set of 30 clinical comorbidities (26 medical, 2 psychiatric, 2 substance use) associated with in-hospital mortality (Sharma et al., 2021; Menendez et al., 2014) and length of stay (Kim and LaBelle, 2018). Using the method described by van Walraven et al., weights were assigned to each of the Elixhauser category diagnoses. A weighted comorbidity score (van Walraven score) was calculated to summarize disease burden (van Walraven et al., 2009). The total number of clinical comorbidities (unweighted) and the summary score (weighted) were considered as predictors. To refine the capture of mental health comorbidities and relevant psychosocial and socioeconomic factors, the Agency for Healthcare Research and Quality Clinical Classification Software (AHRQ-CCS) categories for psychiatric disorders, substance use, and psychosocial factors were also added as predictors. Because the dataset contained ICD-9 and ICD-10 codes, the AHRQ-CCS ICD-9 and ICD-10 categories were matched for similarity using expert psychiatrist review, with the final classification labeled with AHRQ-CCS ICD-10 categories (Suppl. Table 2). Each diagnostic category was labeled for presence at index hospitalization (episode diagnosis) and presence at any encounter preceding index hospitalization (historical diagnosis).

Table 1
Characteristics of patient populations in the derivation (INSIGHT-CRN) and validation (LA-xDR) sets.

Characteristics	Derivation Set		Validation Set	
Ethnicity	N	%	N	%
Non-Hispanic	55,275	47.3%	1260	86.2%
Hispanic	24,788	21.2%	201	13.8%
Other or Unknown	36,698	31.4%	–	
Race				
White	–		1,181	80.8%
Non-White	–		280	19.1%
Age				
18-39	29,610	25.4%	204	14.0%
40-64	60,282	51.6%	693	47.4%
≥65	36,184	31.0%	564	38.6%
Psychiatric Diagnoses				
Depressive disorders	47,163	40.4%	632	43.3%
Bipolar and related disorder	41,785	35.8%	122	8.4%
Schizophrenia spectrum and other psychotic disorders	24,814	21.3%	403	27.6%
Anxiety disorder	7,953	6.8%	112	7.7%
Trauma- and stressor-related disorder	5,867	5.0%	79	5.4%
Comorbid Medical Conditions				
Hypertension, uncomplicated	29,683	25.4%	907	62.1%
Chronic pulmonary disease	25,735	22.0%	416	28.5%
Cardiac arrhythmia	23,864	20.4%	767	52.5%
Fluid or electrolyte disorder	21,434	18.4%	812	55.6%
Hypertension, complicated	18,843	16.1%	20	1.4%
Renal failure	18,471	15.8%	545	37.3%
Diabetes, uncomplicated	16,441	14.1%	204	14.0%
Substance Use Disorder				
Alcohol-related disorders	23,385	20.0%	252	17.2%
Tobacco-related disorders	19,847	17.0%	392	26.8%
Opioid-related disorders	4,753	4.1%	77	5.3%
Stimulant-related disorder	2,974	2.5%	62	4.2%
Medications				
Anxiolytics	49,175	42.1%	414	28.3%
Antipsychotics	47,563	40.7%	352	24.1%
Antidepressants	46,911	40.2%	443	30.3%
Mood Stabilizers	16,593	14.2%	60	4.1%

2.4. Outcome

The primary outcome was hospital readmission for suicide attempt or intentional self-harm within one year following discharge. We restricted the outcome to within one year to increase sensitivity to capture risk factors for self-harm attempts after discharge. The outcome was considered present if the individual was (1) medically hospitalized and (2) the rehospitalization was for a suicide attempt or self-harm. Suicide attempt and self-harm were defined by ICD-9 and ICD-10 codes specified in the 2018 National Health Statistics Report of the Center for Disease Control and Prevention (Hedegaard et al., 2018). The ICD-9 and ICD-10 codes corresponding to the outcome definition are listed in Suppl. Table 4.

2.5. Statistical analysis

2.5.1. Model building

A classification and regression tree (CART) model was developed and tested using the INSIGHT-CRN dataset. CART is a well-established machine learning classifier that creates a binary decision tree (Gordon et al., 1984; Ma, 2018). The tree splits the data into increasingly homogenous groups and selects combinations of potential explanatory variables that can be categorical and/or numeric. Advantages of CART include flexibility to handle multiple data types, ease of clinical interpretation (graphical representation of the tree), and ready handling of rare outcomes (class imbalance) and missing values (Steinberg, 2009). Details of CART methodology have been described in detail elsewhere. CART models have been previously applied to EHR data to successfully

Table 2
Odds of readmission for suicide attempt or self-harm stratified by risk group and study sample.

Predictor	Derivation Set				Validation Set			
	Counts			OR[a] (95%CI)	Counts			OR (95%CI)
	Total	SA/SH[b]	No SA/SH		Total	SA/SH	No SA/SH	
Elixhauser Comorbidities < 2								
Age < 62	317,390	13,330	304,060	1.11 (1.08–1.13)	300	12	288	2.73 (1.48–5.01)
Age ≥ 62	373,432	10,082	363,350	0.61 (0.60–0.63)	200	3	197	0.93 (0.29–2.95)
Elixhauser Comorbidities ≥ 2								
Any History of SA/SH	68,739	7,080	61,659	3.10 (3.02–3.18)	189	41	148	25.67 (16.97–38.84)
No History of SA/SH								
≥1 Hospitalizations[3]	280,405	9,044	271,361	0.79 (0.77–0.80)	5,195	46	5,149	0.25 (0.17–0.36)
No Hospitalizations	375,981	15,685	360,296	1.10 (1.08–1.12)	1,330	14	1,316	0.54 (0.31–0.95)
Total	1,415,947	55,221	1,360,726		7,214	116	7,098	

[a] OR (95% CI): Odds Ratio (95% Confidence Interval).
[b] SA/SH: Suicide attempt or self-harm.

model outcomes during hospitalization (Fonarow et al., 2005; Takahashi et al., 2006) and suicide-related behavior during care transitions (Edgcomb et al., 2020, 2021).

The model was run using Scikit-learn Python toolbox sklearn.tree (Version 0.24.0). Equal-weighted priors were implemented due class imbalance (class_weight = 'balanced'). Tree splits were determined using the Gini index. The complexity parameter optimized the trade-off between tree complexity and misclassification (rpart). Missing values in the derivation set were imputed through corresponding medians. The proportion of missing data for each predictor category is provided in Suppl. Table 3. Tree stability was approximated via bootstrapping and examination of the percentage of trees sharing the first split variable and the number of different variables selected for first split.

2.5.2. Model validation

The model was internally validated using ten-fold cross-validation, such that all tenths of the derivation data were used for both training and testing the algorithm. Cross-validation was used to estimate the future performance of the classifier and generate confidence intervals around model performance (Kohavi, 1995). To ensure replicability, a set seed was used ('random_state = seed'). The out-of-fold performance was measured by the area under the receiver operating curve (AUC), sensitivity, specificity, accuracy, positive predictive value, and negative predictive value. Given the difference in the size of the datasets, tree branches were examined for numerator and denominator sample size, and the tree was pruned to omit branches with very low sample size. Next, tree branches were iteratively pruned to optimize sensitivity. As different base rates in outcome were expected across the derivation and validation datasets, the odds ratio of the outcome of interest was ascertained for each branch by comparing the in-leaf odds of outcome to the out-of-leaf odds of the outcome.

3. Results

3.1. Study cohort characteristics

The characteristics of the INSIGHT-CRN (derivation) and LA-xDR (validation) populations are summarized in Table 1. The derivation set was younger (median age 56.5 years SD 12.7 vs. 58.7 years SD 17.7) and had fewer medical comorbidities (median van Walraven score 19.5 IQR 11–28 vs. 24 IQR 15–35) than the validation set. The readmission rate was 3.9% (55,221/1,415,947) for suicide attempt or self-harm in the derivation set with a median time to readmission of 15.5 days (IQR 7–21.5) and 1.6% (116/7,214) in the validation set with a median time to readmission of 36 days (IQR 12–102).

3.2. Predictive model

The classification model predicted 71% (39,419/55,221) of rehospitalizations for suicide attempt or self-harm with area under the curve (AUC) 0.73 (Confidence Interval [95%CI] 0.68–0.74), accuracy 0.82 (95%CI 0.71–0.83), sensitivity 82.6% (95%CI 81.2–84), and specificity 83.1% (95%CI 81.7–84.5). The final pruned tree model displaying the risk of readmission for suicide attempt or self-harm in each group is presented in Fig. 1. Across 100 bootstrap replications, nine variables were chosen for the first split, with 67.3% of trees generated sharing the same first split variable. The full classification model is presented in Suppl. Figure 2.

The highest risk group consisted of individuals with two or more comorbid medical conditions and a history of suicide attempt or self-harm prior to index hospitalization (Odds Ratio [OR] 3.10, 95% Confidence Interval [95%CI] 3.02–3.18) (Table 2). In the validation set, this group was also at significantly increased risk (OR 25.67, 95%CI 16.97–38.84), with many cases falling within this leaf relative to the sample size of total case positives (41/116 or 35.3% of suicide attempts). The second highest-risk group consisted of individuals with less than two comorbid medical conditions and age less than 62 years old (OR 1.11, 95%CI 1.08–1.13). In the validation set, this group was also at increased risk (OR 2.73, 95%CI 1.48–5.01).

At lower risk were individuals with two or more comorbid medical conditions, no history of suicide attempt or self-harm, and one or more all-cause hospitalizations in the past year (OR 0.79, 95%CI 0.77–0.80). In the validation set, this group was also at lower risk (OR 0.25, 95%CI 0.17–0.36). Also at lower risk were individuals with less than two comorbid medical conditions and age greater than 62 years old (OR 0.61, 95%CI 0.60–0.63); though this did not reach significance in the validation set (OR 0.93, 95%CI 0.29–2.95).

Individuals with two or more comorbid medical conditions, no history of suicide attempt or self-harm, and no hospitalizations in the past year were at elevated risk in the derivation set (OR 1.10, 95%CI 1.08–1.12). However, in the validation set, these individuals were at lower risk (OR 0.54, 95%CI 0.31–0.95).

4. Discussion

In this study of over 1.4 million hospitalizations of adult male medical inpatients with mental illness, risk for self-harm after discharge was highest among those with two or more comorbid health conditions and a history of self-harm. Also, at elevated risk were men younger than 62 years old with less than two comorbid health conditions. Consistent with risk models emphasizing the connectedness of mental and physical illness in the emergence of self-harm after medical illness (Kleespies et al., 2009; Drake et al., 2016), global comorbidity burden (as defined

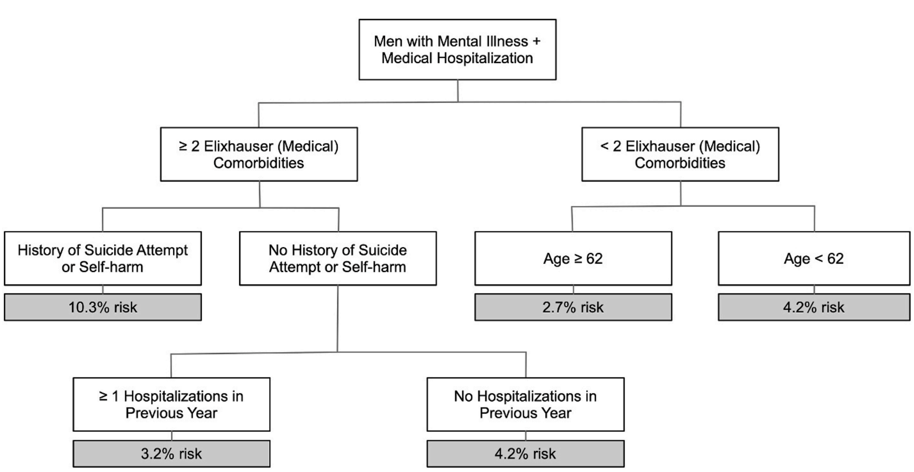

Fig. 1. Classification tree stratifying risk of suicide attempt and self-harm following medical hospitalization among men with serious mental illness. This tree displays common combinations of risk factors identified in both the derivation (INSIGHT-CRN) and validation (LA-xDR) datasets. The complete classification tree for the derivation set is presented in the supplemental digital content. Percent risk refers to the percentage of hospitalizations followed by rehospitalization for suicide attempt and self-harm within one year. Each pathway from root to a leaf node is translated into a series of "if-then" rules that are applied to classify observations. Elixhauser diagnoses refer to the number of standardized comorbidity conditions defined by International Classification of Disease (ICD) codes comprising the Elixhauser Comorbidity Index.

by the number of Elixhauser Comorbidity Index categories comprising 26 medical, 2 substance use, and 2 psychiatric category conditions) was a more robust discriminator of risk than any individual mental health or substance use category condition alone.

We observed that men with greater comorbidity burden experienced different risk factors for self-harm than men with fewer health conditions. There are well-known associations of suicide risk with many physical illnesses, including but not limited to epilepsy (Christensen et al., 2007), myocardial infarction (Larsen et al., 2010), allergy (Qin et al., 2011), and stroke (Eriksson et al., 2015). Declining health (Marusic and Goodwin, 2006), urgent need for medical attention (Costanza et al., 2020), medical hospitalization (Qin et al., 2013), and global comorbidity burden (Edgcomb et al., 2020) are all correlated with risk of self-harm. Previous studies have also established that while some predictors of self-harm are universal, antecedents also vary based on clinical characteristics (e.g., psychiatric comorbidity [Jiang et al., 2021]) and psychosocial complexity (e.g., homelessness [Eynan et al., 2002]). The findings of this study add further evidence that antecedents of self-harm differ with varying burdens of medical illness (Hughes and Kleespies, 2001). This is in keeping with previous work implicating hopelessness, functional impairment, burdensomeness, and inadequacy of treatment as significantly destabilizing in the context of the higher burden of medical illness (Kaplan et al., 2007).

The current work provides additional evidence of sex-specific predictors of self-harm in medically ill populations. Previous research has identified specific medical illnesses, such as liver disease and malignancy, as differentially correlated with self-harm risk in men compared with women (Erlangsen et al., 2015). Gradus et al. (2020) were among the first to use machine learning methods to identify sex-specific risk profiles for suicide among a civilian population. Machine learning has subsequently been applied to sex-specific risk factors among high-risk populations, such as persons with substance use disorders (Adams et al., 2021). Edgcomb et al. (2021) studied women with mental illness following medical hospitalization and identified pregnancy-related mental disorders as an antecedent of suicide-related behavior. The findings of the present study add to this recent literature on sex-specific antecedents of self-harm in the high-risk population of individuals with medical and psychiatric illness. We observed that antecedents of self-harm in men differed from previous work describing risk in women (Edgcomb et al., 2021), including an older age threshold defining risk groups (62 years old for men vs 55 years old previously described for women).

In this study population, men with prior self-harm had three times the risk of post-discharge suicide-related behavior compared to men without prior attempts. However, few general medical inpatients, even those with serious mental illness, are asked about prior self-harm during non-behavioral health-related admissions (García de la Garza et al., 2021). The observed frequency of readmission for a suicide attempt after medical hospitalization suggests that screening for prior self-harm should be considered for medical inpatients with mental health conditions.

5. Limitations

Cautious interpretation of the study results is warranted given the known limitations of EHR datasets and classification models derived from these data. There are several limitations to the data sources used. First, the sample consisted of a high-risk population of adult men with serious mental illness and medical hospitalization, and the results may not generalize to lower risk populations. Second, the study did not capture deaths outside of the hospital or the spectrum of self-harm subthreshold for the medical hospital admission. Third, data for this study were derived from networks affiliated with urban populations and may not generalize to rural or non-U.S. samples. Fourth, due to high missingness on gender identity variables, we used natal sex to identify males, which obfuscates the identification of gender non-binary and trans individuals, who experience markedly elevated risk of suicide (Clements-Nolle et al., 2006) and merit further study. Fifth, unlike claims data research, EHR data are from open health care systems and do not capture services used outside participating hospitals. Moreover, many well-known risk factors were not possible to measure (psychosocial stressors, lethality of prior attempts, family history of suicidal behavior, etc.). Finally, completed suicide, non-fatal attempts, and other intentional harm that did not result in medical care were not captured.

There are also limitations of the classification model. We intentionally select CART as a non-parametric technique to produce an interpretable visualization of predictors. Tree instability is a known limitation of CART and can create a high variance in a tree structure with changes to the dataset (Miglio and Soffritti, 2004). Ensemble methods that combine multiple trees into a single model increase predictive power and stability but reduce the interpretability of the relationship between predictors and outcomes. Before embedding a classification model in real-world settings, it would be prudent to test and compare alternate modeling approaches, including those optimized for stability.

6. Conclusions

Among male medical inpatients with serious mental illness, the risk for self-harm after medical hospital discharge was greatest among men with high global comorbidity and a history of self-harm. Overall comorbidity burden was the most robust discriminator of risk, more so than any mental health or substance use category condition alone. Consideration of both medical and psychiatric comorbidity should be included in suicidal behavior risk stratification during care transitions. Screening for prior self-harm for medical inpatients with mental health conditions, regardless of the primary reason for admission, may help to identify men at elevated risk. Future work should guide further validation of risk groups and pair risk stratification with the assessment of downstream clinical outcomes, healthcare costs, social determinants of health, and disparities in care.

Author's statement

All authors must have materially participated in the research and article preparation.

Rohith Thiruvalluru – (co-first author) conceptualization, methodology, software, validation, formal analysis, data curation, writing -original draft.

Juliet Edgcomb – (co-first author) conceptualization, methodology, software, validation, formal analysis, data curation, writing -original draft.

John Brooks – methodology, supervision, resources, writing -review and editing.

Jyotishman Pathak – methodology, supervision, resources, writing -review and editing.

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Declaration of competing interest

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Appendix A. Supplementary data

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