Increased risk of suicide attempt among patients receiving blood transfusion
A propensity matched analysis

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Abstract

To examine whether the association between blood transfusion and suicide attempt exists.

Utilizing the national insurance database from Taiwan and propensity score matching analysis, the incidence of suicide attempt in a cohort with blood transfusion versus controls was compared.

The key finding is that higher incidence of suicide attempt in blood transfusion than control group (with an adjusted hazard ratio of 1.79 with 95% confidence interval, 1.72–1.88) after adjusted for the covariates.

Patients receiving blood transfusion are an increased risk of subsequent suicide attempt.

Keywords: blood transfusion, propensity, suicide attempt

1. Introduction

Emergent threaten of suicide attempt has been well established, mostly because of the associated high adverse events.[1–3] Importantly, despite the continuous advancement in neuroscience as well as in the knowledge of human behaviors pathophysiology, currently suicide represents a puzzling challenge.[4] In addition, the involvement of sensory perception which is implicated in emotional processes and negative clinical outcomes includes suicidal behavior.[5] The unique sensory processing patterns of individuals have been reported as crucial factors in determining outcomes in the clinical practice.[5] In this case, early detection of and risk stratification for suicide attempt is of paramount importance, not only to attenuate the risk of suicide behavior related complication in an individual, but also to decrease the burden of society from the public health perspective.[1–3]

Blood transfusion is a common medical behavior, either in medical or surgical condition.[6,7] Nonetheless, whether the association between blood transfusion and risk of suicide attempt exist remained unknown. Thus, using a big database analysis, this large scale epidemiology investigation deals with an increasing problem and try to get information about the risk of suicide attempt in the blood transfusion group.

2. Methods

2.1. Data source

Data were extracted from the Longitudinal Health Insurance Database 2013, which was randomly sampled from the National Health Insurance Research Database (NHIRD). To preserve privacy, the de-identification process was applied to the claims data of 1 million residents who had resided in Taiwan, and the distribution of age, sex, the annual number of live births, and average insured premiums in Longitudinal Health Insurance Database 2013 was not significantly different from those in the NHIRD database. To identify diagnoses, the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) was used. The cohort study was approved by the Research Ethics Committee at China Medical University and Hospital in Taiwan (CMUH-104-REC2-115-CR4).

2.2. Study population

Cases of subjects who received a blood transfusion were defined based on the following order codes: 93001C, 93002C, 93003C, and 93019C. The earliest blood transfusion date was used as the index date. Subjects aged less than 20 years or with suicide attempt (ICD-9-CM: E950-E959) before the index date were not included in the study. A total of 62,699 subjects who had blood transfusions were matched with 62,699 subjects who did not

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have blood transfusions between January 1st, 2000 and December 31st, 2012 using propensity score matching in a 1:1 ratio by index year, sex, age, and comorbidities. The end date of the observation period was defined as the end of 2013 or the censored time on which individuals were diagnosed with suicide attempt, died, emigrated or discontinued enrolment from NHIRD.

2.3. Comorbidities

Some suicide attempt-related comorbidities were listed below: diabetes (ICD-9-CM: 250), hypertension (ICD-9-CM: 401 to 405), hyperlipidemia (ICD-9-CM: 272), coronary artery disease (ICD-9-CM: 410 to 413, 414.01 to 414.05, 414.8, and 414.9), peripheral vascular diseases (ICD-9-CM: 443 and 444), congestive heart failure (ICD-9-CM: 428, 398.91, and 402.x1), atrial fibrillation (ICD-9-CM: 427.31), chronic obstructive pulmonary disease (COPD) (ICD-9-CM: 491, 492, and 496), sleep disorder (ICD-9-CM: 307.4 and 780.5), anxiety (ICD-9-CM: 300), depression (ICD-9-CM: 296.2, 296.3, 300.4, and 311), bipolar disorder (ICD-9-CM: 296), schizophrenia (ICD-9-CM: 295), head injury (ICD-9-CM: 800 to 804, 850 to 854, and 959.01), posttraumatic stress disorder (ICD-9-CM: 309.81), iron deficiency anemia (ICD-9-CM: 280), stroke (ICD-9-CM: 430 to 438), chronic kidney disease and end-stage renal disease (ICD-9-CM: 585), alcohol-related illness (ICD-9-CM: 291, 303, 305, 571.0, 571.1, 571.2, 571.3, 790.3, A215, and V11.3), cirrhosis (ICD-9-CM: 571), GI bleeding (ICD-9-CM: 530 to 535, 562.12, 562.13, 569.3, 569.85, 578, 455.2, 455.5, and 455.8), surgery (ICD-9-CM Procedure Code: 01 to 99), cancer (ICD-9-CM: 140 to 208), autoimmune diseases (ICD-9-CM: 245.2, 250.01, 340, 358, 555.9, 556.9, 579, 696.0, 696.1, 710.1, and 710.2), and thyroid disease (ICD-9-CM: 240 to 242 and 244 to 246).

2.4. Statistical analysis

To describe the distributions of the continuous and discrete variables, frequency counts and percentages were used for discrete data and mean values and standard deviations were used for continuous data. To determine whether the distributions of variables in the case cohort were significantly different from those in the comparison cohort, the standardized mean difference was used. Values of standardized mean difference less than or equal to 0.1 indicate negligible differences between the 2 cohorts. Cox proportional hazard model were performed to assess the risk of developing suicide attempt in individuals with and without blood transfusion. Hazard ratios with 95% confidence intervals (95% CIs) were estimated to measure the association of suicide attempt with blood transfusion, and adjusted hazard ratios with 95% CIs were estimated as well. Confounding variables for adjustment included age, sex, comorbidities of diabetes, hypertension, hyperlipidemia, congestive heart failure, sleep disorder, anxiety, depression, bipolar disorder, schizophrenia, head injury, iron deficiency anemia, chronic kidney disease and end stage renal disease, alcohol-related illness, cirrhosis, GI bleeding, surgery, and autoimmune diseases. The plot of the Kaplan–Meier (KM) estimator for incidence of suicide attempt and the log-rank test for difference testing were applied to depict and test the incidence rate difference between the 2 cohorts. All statistical analyses were conducted using SAS 9.4 software (SAS Institute Inc., Cary, NC). The KM curves were plotted by R software. The level of statistical significance was set at a two-tailed P value less than .05.

3. Results

3.1. Baseline characteristics

In the case cohort, there were 31.5%, 24.6%, and 44.0% of subjects in the ≤49 age group, 50 to 64 group, and ≥65 age group, respectively. In the comparison cohort, there were 27.7%, 29.5% and 42.8% of subjects in the ≤49 age group, 50 to 64 group, and ≥65 age group, respectively. The average age was 59.7 ± 17.6 in the case cohort and 59.9 ± 16.4 in the comparison cohort. The case cohort consisted of 50.0% of females and 50.0% of males, and the comparison cohort consisted of 50.1% of females and 49.9% of males. The percentages of patients with any of comorbidities in the case cohort were not significantly different from those in the comparison cohort because standardized mean differences were all less than 0.1. All results mentioned above were summarized in Table 1.

3.2. Stratified analysis to assess the association between suicide attempt and blood transfusion

No matter what age group subjects belonged to, the risk of getting suicide attempt was significantly higher in individuals with blood transfusion when compared to individuals without blood transfusion (aHR, 1.96 with 95% CI, 1.81–2.12 in the ≤49 age group; aHR, 3.16 with 95% CI, 2.89–3.46 in the 50–64 age group; aHR, 1.08 with 95% CI, 1.00–1.15 in the ≥65 age group). Females and males with blood transfusion also had higher risks of developing suicide attempt than females and males without blood transfusion (aHR, 1.87 with 95% CI, 1.76–1.99 in females; aHR, 1.74 with 95% CI, 1.63–1.85 in males). For participants with any of comorbidity listed above, there was a higher risk of diagnosed suicide attempt after blood transfusion (aHR, 1.78 with 95% CI, 1.70–1.86). All results mentioned above were summarized in Table 2.

3.3. Trend analysis and KM plot to assess the association between suicide attempt and the number of annual blood transfusion

Compared to participants without blood transfusion, the more annual blood transfusions participants received, the higher risk of developing suicide attempt participants had (aHR, 1.28 with 95% CI, 1.21–1.34 for the number of annual blood transfusion ≤1; aHR, 6.27 with 95% CI, 5.90–6.67 for the number of annual blood transfusion ≥2). The value of p for trend was also statistically significant. All results mentioned above were summarized in Table 3. Based on the cumulative incidence of suicide attempt for subjects with or without blood transfusion, there was a statistically significant difference between the 2 cohorts on the risk of getting suicide attempt. The KM plot was shown in Figure 1.

4. Discussion

This is, in summary, a study aimed to examine whether the association between blood transfusion and suicide attempt exists. We stressed the higher incidence of suicide attempt in blood transfusion than control group after adjusted for the covariates and concluded that patients receiving blood transfusion are an increased risk of subsequent suicide attempt.

Overall, the advantage is clearly that using a nation-wide database, there is little bias in terms of prevalence which is usually

Table 1

Demographic characteristics and comorbidities in cohorts with and without blood transfusion.

	Blood transfusion		Standard mean difference[*]
	No N = 62699	**Yes** N = 62699	
Variable			
Age, yr			
≤49	17381 (27.7)	19722 (31.5)	0.08
50–64	18466 (29.5)	15409 (24.6)	0.11
65+	26852 (42.8)	27568 (44.0)	0.02
Mean ± SD	59.9 ± 16.4	59.7 ± 17.6	0.01
Sex			
Female	31439 (50.1)	31333 (50.0)	0.03
Male	31260 (49.9)	31366 (50.0)	0.03
Comorbidity			
Diabetes	11306 (18.0)	11105 (17.7)	0.008
Hypertension	31323 (50.0)	30611 (48.8)	0.023
Hyperlipidemia	16434 (26.2)	15952 (25.4)	0.018
Coronary artery disease	11954 (19.1)	11747 (18.7)	0.008
Peripheral vascular disease	1660 (2.65)	1665 (2.66)	0.000
Congestive heart failure	5350 (8.53)	5486 (8.75)	0.008
Atrial fibrillation	1224 (1.95)	1272 (2.03)	0.005
Chronic obstructive pulmonary disease	14710 (23.5)	1498 (23.6)	0.003
Sleep disorder	15166 (24.2)	14855 (23.7)	0.012
Anxiety	12948 (20.7)	12627 (20.1)	0.013
Depression	4130 (6.59)	3995 (6.37)	0.009
Bipolar disorder	388 (0.62)	365 (0.58)	0.005
Schizophrenia	450 (0.72)	419 (0.67)	0.006
Head injury	3888 (6.20)	3680 (5.87)	0.014
Posttraumatic stress disorder	17 (0.03)	11 (0.02)	0.006
Iron deficiency anemia	2205 (3.52)	2152 (3.43)	0.005
Stroke	6330 (10.1)	6610 (10.5)	0.015
CKD and ESRD	1876 (2.99)	2289 (3.65)	0.037
Alcohol-related illness	4617 (7.36)	4396 (7.01)	0.014
Cirrhosis	15731 (25.1)	15584 (24.9)	0.005
GI bleeding	1442 (2.30)	1529 (2.44)	0.009
Surgery	60486 (96.5)	59998 (95.7)	0.040
Cancer	5386 (8.59)	5586 (8.91)	0.011
Autoimmune diseases	3094 (4.93)	3023 (4.82)	0.005
Thyroid disease	2648 (4.22)	2547 (4.06)	0.008

[*] A value of standard mean difference equals 0.1 or less, which indicates a negligible difference in means between blood transfusion and matched cohorts.

Table 2

Incidence of suicide attempt by age, sex, and comorbidity and Cox model measured hazards ratio for patients with blood transfusion compared those without blood transfusion.

	Blood transfusion							
	No			**Yes**				
Variables	Event	PY	Rate[#]	Event	PY	Rate[#]	Crude HR (95% CI)	Adjusted HR[a] (95% CI)
Overall	25	336827	0.74	34	241173	1.41	1.90 (1.81, 1.99)[***]	1.79 (1.72, 1.88)[***]
Age, yrs								
≤49	9	106737	0.84	17	97579	1.74	2.07 (1.90, 2.25)[***]	1.96 (1.81, 2.12)[***]
50–64	5	102674	0.49	9	60554	1.49	3.05 (2.78, 3.35)[***]	3.16 (2.89, 3.46)[***]
65+	11	127416	0.86	8	83039	0.96	1.12 (1.04, 1.20)[**]	1.08 (1.00, 1.15)[*]
Sex								
Female	13	172232	0.75	19	133138	1.43	1.89 (1.77, 2.02)[***]	1.87 (1.76, 1.99)[***]
Male	12	164595	0.73	15	108035	1.39	1.90 (1.78, 2.03)[***]	1.74 (1.63, 1.85)[***]
Comorbidity[$]								
No	0	6403	0.00	1	3523	2.84	–	–
Yes	25	330424	0.76	33	237649	1.39	1.84 (1.75, 1.92)[***]	1.78 (1.70, 1.86)[***]

PY = person-years; Rate[#], incidence rate, per 10,000 person-years; Crude HR represented hazard ratio; [a]Variables found to be statistically significant in the univariable model were further examined in the multivariable model. Adjusted for age, sex, comorbidities of diabetes, hypertension, hyperlipidemia, congestive heart failure, sleep disorder, anxiety, depression, bipolar disorder, schizophrenia, head injury, iron deficiency anemia, CKD and ESRD, alcohol-related illness, cirrhosis, GI bleeding, surgery, and autoimmune diseases.

[$] Individuals with any comorbidity of diabetes, hypertension, hyperlipidemia, coronary artery disease, peripheral vascular disease, congestive heart failure, atrial fibrillation, chronic obstructive pulmonary disease, sleep disorder, anxiety, depression, bipolar disorder, schizophrenia, head injury, posttraumatic stress disorder, iron deficiency anemia, stroke, CKD and ESRD, alcohol-related illness, cirrhosis, GI bleeding, surgery, cancer, autoimmune diseases, and thyroid disease were classified into the comorbidity group.

[*] P < .05.
[**] P < .01.
[***] P < .001.

Table 3

Hazard ratios and 95% confidence intervals of suicide attempt risk associated with the number of annual blood transfusion during the follow-up period.

	No. of Event	Crude HR (95% CI)	Adjusted HR[a] (95% CI)
Non-blood transfusion	25	1 (Reference)	1 (Reference)
Times of blood transfusion			
≤1	22	1.36 (1.30, 1.44)***	1.28 (1.21, 1.34)***
≥2	12	6.67 (6.28, 7.09)***	6.27 (5.90, 6.67)***
P for trend		<.001	<.001

Crude HR, relative hazard ratio; [a]Variables found to be statistically significant in the univariable model were further examined in the multivariable model. Adjusted for age, sex, comorbidities of diabetes, hypertension, hyperlipidemia, congestive heart failure, sleep disorder, anxiety, depression, bipolar disorder, schizophrenia, head injury, iron deficiency anemia, CKD and ESRD, alcohol-related illness, cirrhosis, GI bleeding, surgery, and autoimmune diseases.
*** $P < .001$.

present in studies performed in tertiary centers. The problem is clearly identified and methods are clearly explained. Moreover, the large number of patients included in the analysis is one of the principal strengths of the investigation. The discussion consistently relates the key findings and the analysis is balanced.

The key finding of increased incidence of suicide attempt in blood transfusion group than controls was clearly demonstrated and this association is even more profound in the subgroup of female gender, patients aged 50 to 64 years, and with comorbidity. Furthermore, the association is even stronger in a relatively dose-dependent manner. Such observation might be of clinical significance, since more attention is necessary to paid to

this subgroup so that early identification of incident suicide attempt and subsequent management strategy can be instituted.

Although early studies have clearly concluded that several groups of patients are at an increased risk of subsequent suicide attempt.[8–12] To our knowledge, whether this phenomenon can be extended to individuals receiving blood transfusion remained undetermined. Since blood transfusion is a common therapy, and subjects receiving blood transfusion is increasing in number. From the public health perspective, it is reasonable to understand whether this group is susceptible to incident suicide attempt. Although it would be helpful to learn more about the causal relationship between blood transfusion and suicide attempt. A
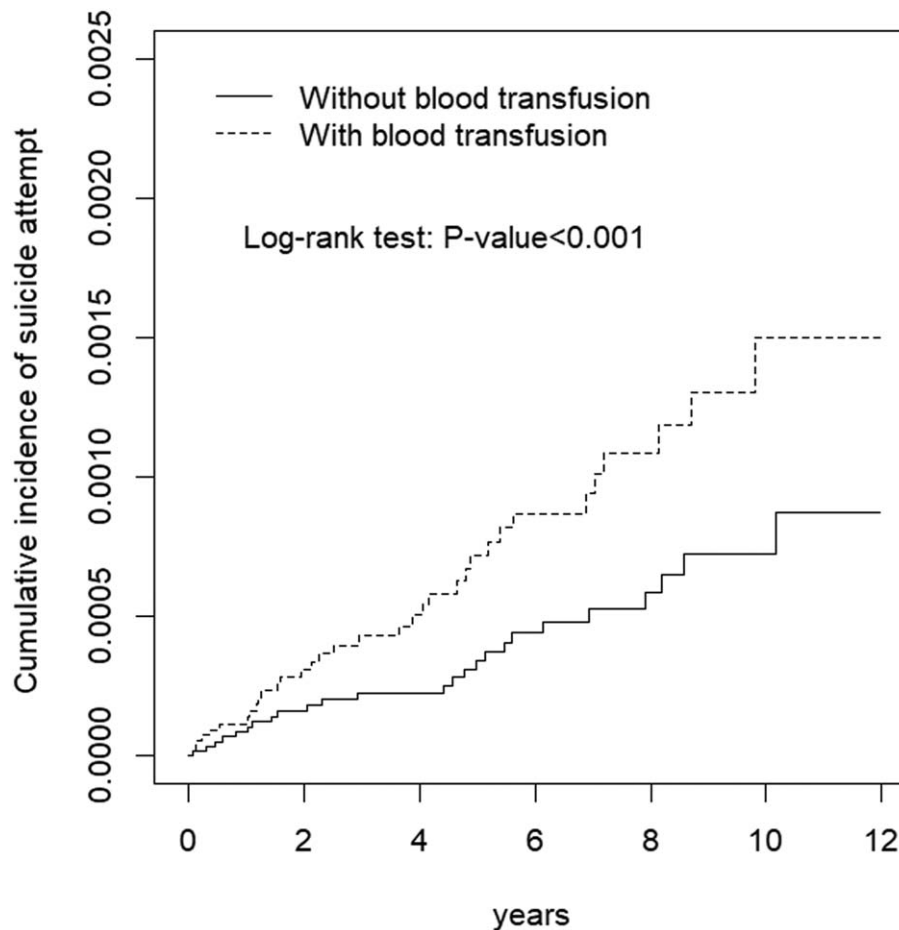
Figure 1. Cumulative incidence curves of suicide attempt for patients with (dashed line) or without (solid line) blood transfusion.

degree of biological plausibility is relatively difficult to conclude because of the inherent nature of retrospective observational research design. Possible contributing factors underlying the association might be, at least in part, related to endothelial dysfunction, inflammation reaction, oxidative stress.[13–16] Moreover, some researchers might criticize the underlying mechanism underlying this association might be related to the sicker medical condition of patient receiving blood transfusion. However, these factors are well matched between blood transfusion group and controls. Further mechanism exploring studies are highly encouraged.

5. Limitations

Regarding the weaknesses, probably there is a selection bias with using diagnosis code and selecting patients from a large database. For example: patients with blood transfusion due to the same condition have more medical visits and also had more comorbidity that should have also required more medical visits, if you go to see a doctor more times, you are more likely to report psychological discomfort. Also, the study is retrospective, as there is no medication record, it cannot be controlled by this. Moreover, religious beliefs might have an impact on the suicide rates that should also be taken into account. However, such data were lacking in this dataset. Finally, the reported strength of this association might not be so clinically relevant, therefore susceptible to these bias in this study.

6. Conclusion

The risk of suicide attempt in blood transfusion patients was 1.79-fold higher than that of controls.

Author contributions

Analysis: Cheng-Li Lin
Acquisition of data: Cheng-Li Lin.
Conceptualization: Ws Hu.
Data curation: Cheng Li Lin.
Interpretation: Cheng-Li Lin.

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