

Joint effects of risk factors on adverse events associated with adult blood donations

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Abstract

The process for blood donation is considered safe, but some adverse events have been reported. Risk factors for adverse events were assessed in this study.

A retrospective case-control study was conducted to investigate the risk factors for adverse events after blood donation between 2010 and 2013. Variables such as gender, age, body mass index (BMI), donation status, donation volume, donation site, pre-donation systolic blood pressure (SBP), and pre-donation diastolic blood pressure were compared between donors with and without adverse events. Multiple logistic regression analysis was performed to assess the joint effects of age, gender, and donation status on adverse events.

The incidence of adverse events among adult blood donations was 1287/1,253,678 (0.1%). On multivariate logistic regression analysis, blood donors aged <35 years (odds ratio [OR], 2.99, 95% confidence interval [CI], 2.57–3.48), of female gender (OR, 3.30, 95% CI, 2.62–4.15), and with first-time donor status (OR, 6.40, 95% CI, 5.17–7.93), donation of 500 mL (OR, 2.22, 95% CI, 1.83–2.69), predonation SBP <124 mm Hg (OR, 1.25, 95% CI, 1.05–1.48) and BMI <24 kg/m² (OR, 1.67, 95% CI, 1.42–1.96) were associated with increased likelihood of adverse event. Further analysis with joint effects method revealed that first-time female donors aged <35 years are associated with the highest odds of adverse events when compared with repeat male donors aged ≥35 years (OR, 100.57, 95% CI, 48.45–208.75).

The findings of our study should prove useful in identifying donors at risk and planning appropriate strategies for the prevention of adverse effects.

Abbreviations: AMT = applied muscle tension, AT2R-bound Ang II = angiotensin II type two receptor, BMI = body mass index, BP = blood pressure, CIs = confidence intervals, DBP = diastolic blood pressure, EBV = estimated blood volume, Hb = hemoglobin, ORs = odds ratios, RAS = renin angiotensin system, RSNA = renal sympathetic nervous activity, SBP = systolic blood pressure, SOP = standard operating procedure, VVR = vasovagal reaction, VVS = vasovagal syncope, WB = whole blood.

Keywords: adverse events, vasovagal reactions, whole blood donations

1. Introduction

Volunteer blood donors must be healthy to donate blood. Donating blood is generally safe, but during or upon completion of the blood donation process adverse events may occur.

Adverse events of blood donation can be divided into 2 types: acute reaction and chronic reaction. Hematoma or nerve damage may occur during venipuncture. The most common acute

reaction is vasovagal reaction (VVR) or vasovagal syncope (VVS). VVS is a syncope syndrome, characterized by transient loss of consciousness, associated with hypotension and relative bradycardia.^[1] VVS can result in an unexpected fall which can lead to injuries. The prevalence of adverse events of blood donation has been reported to be as high as 1%. Among them, VVRs account for approximately 75%^[2] VVRs and VVS are

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thought to be caused by physical and psychological inducements.^[3,4] Chronic adverse events such as iron deficiency may occur in regular blood donors.^[5]

The results of this study showed that young blood donors, first-time donors, and donors with low body mass index (BMI), low estimated blood volume (EBV), high blood pressure (BP) before blood collection, rapid pulse, or insufficient amount of sleep are associated with risk of VVR.^[6] Factors linked to the risk of VVR can be broadly divided into 3 categories – observable donor characteristics (eg, age, gender), unobservable donor characteristics (eg, low BP, insufficient sleep duration), and contextual factors (eg, spring season, longer bleeding time).^[7] VVRs can lead to serious accidents after blood donation. The highest injury rates per donation, occurring in ambulating donors, are 0.07 and 0.09/1000 donations for male and female donors, respectively.^[8]

There are 2 donation types in Taiwan: whole blood (WB) and apheresis platelets. Previous studies have shown that VVRs are more frequent after WB donation.^[9] Depending on the criteria for eligible blood donors, WB donations are collected in volumes of 250 mL or 500 mL.

There are different selection criteria, donation volumes, and policies for reducing the adverse events of blood donations in different countries. Therefore, the incidences of adverse events may differ among countries. Although only a small number of blood donors experience adverse events after WB donation, such events may threaten the health of donors or discourage them from donating again. Therefore, preventing adverse events in blood donors is an important issue. To reduce the risk of adverse events and maintain the blood supply, the aim of this retrospective study was to investigate the incidences of adverse events and their important risk factors such as age, gender, donation status, and BP to improve the safety of the blood donation process.

2. Materials and methods

2.1. Study population and design

There was no change in the standard procedure for blood donations during this study. We determined the risk factors of adverse events and analyzed the joint effects of major risk factors for WB donations as the incidence of adverse events was higher among WB donations than among other type of donations. The aim of this study was to identify the risk factors most associated with adverse events for educating blood donation staff to identify donors who are at risk and to reduce the incidences of adverse events.

The population of the Taichung Blood Center's service area, located in central Taiwan, is about 4.5 million with approximately 350,000 blood donations received each year. This center serves more than 150 medical institutions. There are 2 types of blood donation: WB and apheresis platelets. The criteria for blood donors are in accordance with Taiwan's Ministry of Health and Welfare guidelines.

In Taiwan, blood donors are recommended not to fast. If donors have been fasting, we ask them to eat a meal before donation. When the interval between the last meal and donation time is over 4 hours, we offer snacks and milk.

Donor selection was based on blood donor registration forms, which include demographic information such as height, weight, gender, donation history, and date of birth. Interview regarding lifestyle and habits and a limited physical examination such as BP measurement were conducted. Those reporting insufficient sleep were deferred from donating blood. The health status question-

naire included present and past medical/surgical history. Blood donors are required to be from 17 to 65 years old. In Taiwan, the legal adult age is 20. Therefore, in this study, the age group 20 to 65 years was selected.

The criteria for WB donors is a bodyweight of ≥ 50 kg and a hemoglobin (Hb) level of ≥ 13.0 g/dL for males and a bodyweight of ≥ 45 kg and an Hb level of ≥ 12.0 g/dL for females.

Hb screening was based on copper sulfate density. Systolic blood pressure (SBP) was defined as 90 to 160 mm Hg and diastolic blood pressure (DBP) as 50 to 95 mm Hg. Pulse rate was to be between 60 and 100 beats per minute. There were 2 volumes of WB donations, 250 mL and 500 mL. Donation intervals were 2 months for 250 mL and 3 months for 500 mL. The maximum amounts of WB donation were 1500 mL for males and 1000 mL for females per annum, adjusted by date of birth. All the participants in this study were eligible to donate blood. After blood donation, we offered blood donors snacks, coffee, juice or milk and asked them to rest for 10 to 15 minutes. This study was conducted over a 4 year period, from January 1, 2010 to December, 31, 2013.

Subjects with a height of less than 140 cm, weight of more than 130 kg and missing data were excluded.

2.2. Data collection

Donor records were obtained from the Taichung Blood Center. They included collection date, collection status, collection site, donation volume, and so on. To understand whether hot weather is associated with the risk of adverse events, compared to non-hot weather, we defined March to August as hot weather season and September to February as non-hot weather season.

BMI was defined as body mass divided by the square of body height and EBV was calculated using the following equations (height, in meters; weight, in kg).

Female donors: blood volume (L) = $0.3561 (\text{Height})^3 + 0.03308 (\text{Weight}) + 0.1833$

Male donors: Blood volume (L) = $0.3669 (\text{Height})^3 + 0.03219 (\text{Weight}) + 0.6041$

The control group was randomly selected from donors without adverse events at a ratio of 4:1 (control: no adverse events vs. case: adverse events). After excluding donations with missing data, there were 5083 donations in the control group and 1255 donations in the adverse events group in this study. The study recruitment flowchart is shown in Figure 1. The adverse events are summarized occurring during the study period in Figure 2.

Ethics approval was obtained from the Ethical Review Board of the Taiwan Blood Services Foundation (PM-103-TC-131). This research was performed in accordance with "Declaration of Taipei" ethical guidelines.

2.3. Ascertainment of adverse events

Adverse events such as VVRs are reported on standardized forms that include location where the adverse reaction occurred, symptoms, and whether the donor was sent to hospital. Adverse events that occur on-site can be managed by the collection staff, including physicians. Off-site reactions are rarely observed by blood center staff. Off-site reaction information is reported by donors and occasionally accompanied by reports from hospitals or relatives of affected blood donors. Severe cases are sent to hospital for treatment. We kept a systematic record of events and followed upon them. VVRs were classified as mild when donors presented with pallor,

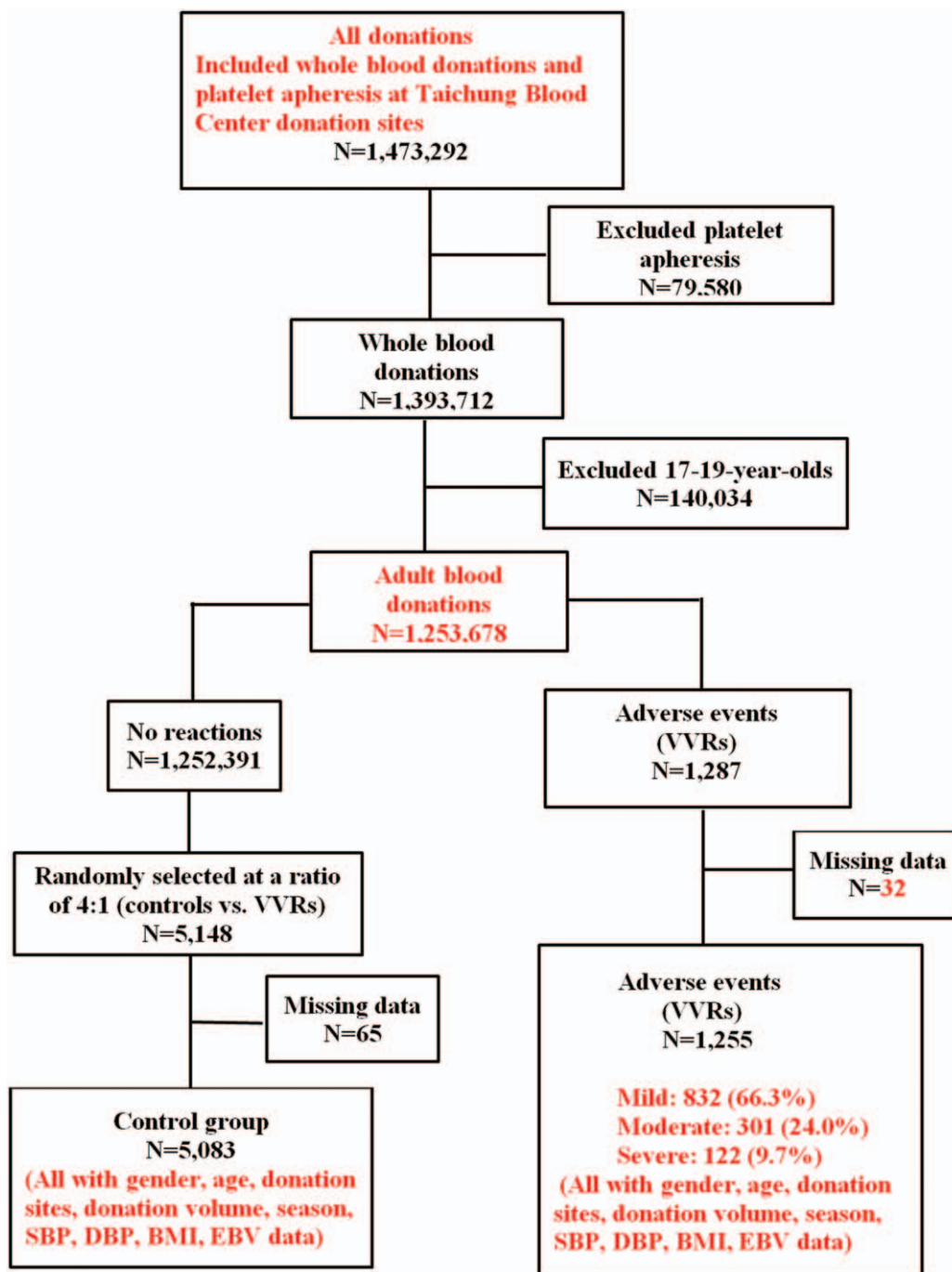


Figure 1. Flowchart of the recruitment procedure. BMI = body mass index, DBP = diastolic blood pressure, EBV = estimated blood volume, SBP = systolic blood pressure.

sweating, dizziness, and fatigue but not loss of consciousness; moderate when there was loss of consciousness for less than 60 seconds, vomiting or hypotension; and severe when there was loss of consciousness for 60 seconds or more, convulsions, rigidity and urine/fecal incontinence. In this study, all VVRs were recorded according to the standard operating procedure.

2.4. Statistical analysis

The variables of age, BMI, predonation SBP, predonation DBP, and EBV were dichotomized by their median values.

All statistical analyses in this study were conducted using SPSS statistical software (SPSS Inc, Chicago, IL; PASW Statistics 18.0). Chi-squared test and *t* test were respectively used for binary variables and continuous variables to compare the baseline demographic characteristics of the case and control groups. A univariate logistic regression model was then used to analyze the strength of association between potential factors and adverse events. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Multiple logistic regression analysis was performed to identify the independent risk factors for adverse reactions to adjust for potential important confounders. At last,

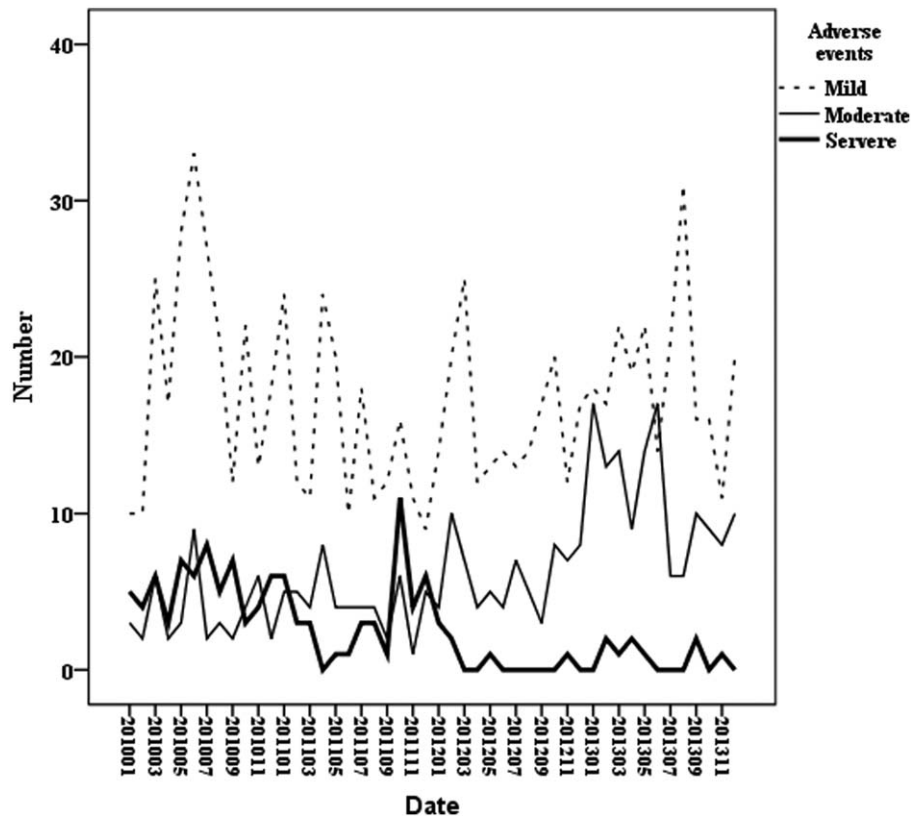


Figure 2. The summary of the adverse events occurring during the study period.

we explored the joint effects of the risk factors with greatest magnitude of strength of association. The P -value of the test was 2-tailed with a level of significance (α) = .05. A P -value of less than .05 indicated statistical significance.

3. Results

3.1. Adverse events and multivariate analysis

During the 4-year study period, 1,473,292 blood donations were enrolled from the Taichung Blood Center. After excluding platelet apheresis donations, the number of WB donations by donors aged 20 to 65 was 1,253,678. Among them, 1,252,391 donations were without adverse event and 1287 were with adverse event. The incidence of adverse events was 1287/1,253,678 (0.1%).

The characteristics of the adverse events and control groups are shown in Table 1. The variables in Table 1 include gender, age, donation status, donation volume, donation site, season, predonation SBP, predonation DBP, BMI, and EBV. Table 1 shows that age <35 years, first-time donor, 500mL donation volume, donation at mobile site, predonation SBP <124 mm Hg, predonation DBP <75 mm Hg, BMI <24 kg/m², and EBV \geq 4085 mL are associated with significantly higher proportions of adverse events when compared with controls (all P < .05). The summary of the adverse events and the characteristics of these donors was showed in Table 3.

Adverse events occurred in donors who were significantly younger (30.28 years old vs 38.03 years old) and had lower mean BMI (23.62 kg/m² vs 24.37 kg/m²), predonation SBP (120.49 mm Hg vs 125.29

mm Hg) and predonation DBP (73.59 mm Hg vs 75.77 mm Hg) (all P < .001). The mean EBV was higher in the adverse events group than in the control group (4255 mL vs 4058 mL) (P < .001) Table 2.

3.2. Donors with adverse events

Although, no deaths occurred among donors with adverse events, adverse events affect the safety of blood donors and decrease donors' willingness to donate again. Thus, understanding risk factors of adverse events is important.

All demographic characteristics converted to dichotomous variables were coded as 0 or 1 by the medium values.

Risk factors identified as predicting a responsive outcome from the donors with adverse events were the age <35 years old (OR = 3.72, 95% CI = 3.72–4.27, P < .001), the first-time donation (OR = 6.41, 95% CI = 5.30–7.74, P < .001), the 500 mL of donation volume (OR = 1.16, 95% CI = 1.02–1.31, P = .023), the mobile of donation sites (OR = 1.62, 95% CI = 1.40–1.87, P < .001), the predonation SBP <124 mm Hg (OR = 1.64, 95% CI = 1.44–1.86, P < .001), the predonation DBP <75 mm Hg (OR = 1.45, 95% CI = 1.28–1.65, P < .001), the BMI <24 kg/m² (OR = 1.36, 95% CI = 1.20–1.54, P < .001), and the EBV \geq 4085 mL (OR = 1.67, 95% CI = 1.47–1.90, P < .001) (Table 4).

Results of multiple logistic regression analysis are shown in Table 5. Multivariate analysis revealed that the age <35 years old (OR = 2.99, 95% CI = 2.57–3.48, P < .001), the female (OR = 2.99, 95% CI = 2.57–3.48, P < .001), the first-time donation (OR = 6.40, 95% CI = 5.17–7.93, P < .001), the 500 mL of donation volume (OR = 2.22, 95% CI = 1.83–2.69, P < .001), the mobile of donation sites (OR = 1.66, 95% CI = 1.42–1.95,

Table 1
Characteristics of study subjects.

Variables	Adverse events n (%)	No adverse events n (%)	P-value*
Gender			.324
Male	720 (57.4%)	2994 (58.9%)	
Female	535 (42.6%)	2089 (41.1%)	
Age, yr			<.001
<35	937 (74.7%)	2247 (44.2%)	
≥35	318 (25.3%)	2836 (55.8%)	
Donation status			<.001
First-time	283 (22.5%)	221 (4.4%)	
Repeat	972 (77.5%)	4862 (95.6%)	
Donation volume, mL			.023
500	523 (41.7%)	1941 (38.2%)	
250	732 (58.3%)	3142 (61.8%)	
Donation sites			<.001
Fixed	268 (21.4%)	1551 (30.5%)	
Mobile	987 (78.6%)	3532 (69.5%)	
Season			.631
Hot weather season (March–August)	667 (53.1%)	2663 (52.4%)	
Non-hot weather season (September–February)	588 (46.9%)	2420 (47.6%)	
Predonation SBP, mm Hg			<.001
<124	750 (59.8%)	2418 (47.6%)	
≥124	505 (40.2%)	2665 (52.4%)	
Predonation DBP, mm Hg			<.001
<75	746 (59.%)	2557 (50.3%)	
≥75	509 (40.6%)	2526 (49.7%)	
BMI, kg/m ²			<.001
<24	715 (57.0%)	2509 (49.4%)	
≥24	540 (43.0%)	2574 (50.6%)	
EBV, mL			<.001
<4085	500 (40.0%)	2670 (52.5%)	
≥4085	755 (60.0%)	2413 (47.5%)	
Adverse events			
Mild	832 (66.3%)		
Moderate	301 (24.0%)		
Severe	122 (9.7%)		

BMI = body mass index, DBP = diastolic blood pressure, EBV = estimated blood volume, SBP = systolic blood pressure.

* P-value from Chi-square test.

$P < .001$), the predonation SBP < 124 mm Hg (OR = 1.25, 95% CI = 1.05–1.48, $P = .011$), and the BMI < 24 kg/m² (OR = 1.67, 95% CI = 1.42–1.96, $P < .001$) appeared to be independent risk factors for adverse events after blood donation.

We further elucidated the cause of differences in adverse events between mobile and fixed sites. For fixed sites, the results of

Table 3
Characteristics of adverse events of study subjects.

Variables	Donation sites	
	Fixed N = 268 (%)	Mobile N = 987 (%)
Gender		
Male	154 (57.4%)	566 (57.3%)
Female	114 (42.6%)	421 (42.7%)
Age, yr		
<35	206 (76.9%)	731 (74.1%)
≥35	62 (23.1%)	256 (25.9%)
Donation status		
First-time	56 (20.9%)	227 (23.0%)
Repeat	212 (79.1%)	760 (77.0%)
Donation volume, mL		
500	116 (43.3%)	407 (41.2%)
250	152 (56.7%)	580 (58.8%)
Season		
Hot weather season (March–August)	138 (51.5%)	529 (53.6%)
Non-hot weather season (September–February)	130 (48.5%)	458 (46.4%)
Predonation SBP, mm Hg		
<124	140 (61.9%)	610 (61.8%)
≥124	128 (38.1%)	377 (38.1%)
Predonation DBP, mm Hg		
<75	166 (61.9%)	580 (59.6%)
≥75	102 (38.1%)	407 (40.4%)
BMI, kg/m ²		
<24	163 (60.8%)	552 (55.9%)
≥24	105 (39.2%)	435 (44.1%)
EBV, mL		
<4085	106 (39.6%)	394 (39.9%)
≥4085	162 (60.4%)	593 (60.1%)
Adverse events		
Mild	173 (64.6%)	659 (64.7%)
Moderate	73 (27.2%)	228 (23.1%)
Severe	22 (8.2%)	100 (10.2%)

BMI = body mass index, DBP = diastolic blood pressure, EBV = estimated blood volume, SBP = systolic blood pressure.

multivariate analysis revealed that age < 35 years (OR = 3.16, 95% CI = 2.29–4.36, $P < .001$), female gender (OR = 1.51, 95% CI = 1.02–2.24, $P = .041$), first-time donation (OR = 11.77, 95% CI = 7.31–18.96, $P < .001$), and 500 mL donation volume (OR = 2.82, 95% CI = 1.86–4.29, $P < .001$) are independent risk factors for adverse events after blood donation (Table 6).

Table 2
Mean biomarkers for donors with and without adverse events.

Variables overall	Adverse events n = 1255 (mean ± SD)	No adverse events n = 5083 (mean ± SD)	P-value*
Age, yr	30.28 ± 9.81	38.03 ± 11.90	<.001
BMI, kg/m ²	23.62 ± 3.52	24.37 ± 3.53	<.001
EBV, mL	4255.18 ± 731.84	4058.46 ± 588.27	<.001
Predonation SBP, mm Hg	120.49 ± 14.76	25.29 ± 15.88	<.001
Predonation DBP, mm Hg	73.59 ± 9.55	75.77 ± 10.36	<.001

BMI = body mass index, DBP = diastolic blood pressure, EBV = estimated blood volume, SBP = systolic blood pressure.

* P-value from 2-sample *t* test.

Table 4**Odds ratios and 95% confidence intervals from univariate logistic regression analysis in the adverse events.**

Demographic characteristics	OR (95% CI)	P-value*
Overall		
Season		.631
Hot weather season (25.75 ± 4.47°C)	1.03 (0.91–1.17)	
Non-hot weather season (21.22 ± 4.96°C)	1.00	
Age, yr		<.001
<35	3.72 (3.72–4.27)	
≥35	1.00	
Gender		.324
Male	1.00	
Female	1.07 (0.94–1.21)	
Donation status		<.001
First-time	6.41 (5.30–7.74)	
Repeat	1.00	
Donation volume, mL		.023
500	1.16 (1.02–1.31)	
250	1.00	
Donation sites		<.001
Fixed	1.00	
Mobile	1.62 (1.40–1.87)	
Predonation SBP, mm Hg		<.001
<124	1.64 (1.44–1.86)	
≥124	1.00	
Predonation DBP, mm Hg		<.001
<75	1.45 (1.28–1.65)	
≥75	1.00	
BMI, kg/m ²		<.001
<24	1.36 (1.20–1.54)	
≥24	1.00	
EBV, mL		<.001
<4085	1.00	
≥4085	1.67 (1.47–1.90)	

BMI = body mass index, CI = confidence interval, DBP = diastolic blood pressure, EBV = estimated blood volume, OR = odds ratio, SBP = systolic blood pressure.

* P-value for testing ORs

For mobile sites, the results of multivariate analysis revealed that age <35 years (OR = 3.20, 95% CI = 2.70–3.79, $P < .001$), female gender (OR = 1.45, 95% CI = 1.19–1.75, $P < .001$), first-time donation (OR = 5.77, 95% CI = 4.57–7.31, $P < .001$), 500 mL donation volume (OR = 2.82, 95% CI = 1.86–4.29, $P < .001$), predonation SBP <124 mm Hg (OR = 1.33, 95% CI = 1.10–1.62, $P = .003$), and BMI <24 kg/m² (OR = 1.21, 95% CI = 1.01–1.43, $P = .035$) are independent risk factors for adverse events after blood donation (Table 7).

Apparently, the independent risk factors of predonation SBP <124 mm Hg and BMI <24 kg/m² contribute more to adverse events at mobile donation sites.

3.3. Joint effects of age, gender, and donation status on adverse events

The ORs of 3 major risk factors (age, gender, and donation status) were analyzed simultaneously as demonstrated in Table 8. Male repeat donors aged ≥35 years were treated as the reference group. Male repeat donors aged <35 years (age effect) were associated with increased odds of adverse events (OR, 2.48, 95% CI, 2.27–3.40), as were male first-time donors aged ≥35 years (donation status effect) (OR, 5.67, 95% CI, 1.71–18.79) and female repeat donors aged ≥35 years (gender effect) (OR, 3.08,

Table 5**Odds ratio and 95% confidence intervals in multivariate logistic regression analysis in the adverse events.**

Demographic characteristics	OR (95% CI)	P-value*
Overall		
Season		.662
Hot weather season (25.75 ± 4.47°C)	1.03 (0.90–1.18)	
Non-hot weather season (21.22 ± 4.96°C)	1.00	
Age, yr		<.001
<35	2.99 (2.57–3.48)	
≥35	1.00	
Gender, yr		<.001
Male	1.00	
Female	3.30 (2.62–4.15)	
Donation status		<.001
First-time	6.40 (5.17–7.93)	
Repeat	1.00	
Donation volume, mL		<.001
500	2.22 (1.83–2.69)	
250	1.00	
Donation sites		<.001
Fixed	1.00	
Mobile	1.66 (1.42–1.95)	
Predonation SBP, mm Hg		0.011
<124	1.25 (1.05–1.48)	
≥124	1.00	
Predonation DBP, mm Hg		0.855
<75	1.02 (0.86–1.20)	
≥75	1.00	
BMI, kg/m ²		<.001
<24	1.67 (1.42–1.96)	
≥24	1.00	

BMI = body mass index, CI = confidence interval, DBP = diastolic blood pressure, EBV = estimated blood volume, OR = odds ratio, SBP = systolic blood pressure.

* P-value for testing ORs.

95% CI, 2.02–4.70). In terms of the joint effects of any 2 of the 3 intermediate risk factors, the magnitude of association became much greater: age and gender effect OR, 9.34, 95% CI, 6.31–13.83; age and donation status effect OR, 14.57, 95% CI, 19.36–115.72; and gender and donation status effect OR, 47.33, 95% CI, 19.36–115.72. Female first-time donors aged <35 years (joint effects of age, gender, and donation status) were associated with increased odds of adverse events compared with male repeat donors aged ≥35 years (OR, 100.57, 95% CI, 48.45–208.75).

4. Discussion

The incidence of adverse events during or after WB donation was 0.1% over a 4-year period. Incidence of adverse events after blood donation was an important quality indicator monitored monthly to set a strategy for lowering the incidences of adverse events.

Our findings showed that the most significant risk factor for adverse events is first-time blood donor. Gender and age were the other 2 significant factors with moderate to strong association. In Taiwan, first-time donors are not recommended to donate 500 mL WB or apheresis platelets to prevent adverse reaction. From 2010 to 2014, 1.86% of males and 0.013% of females aged 20 to 65 years donated 500 mL as first-time donors at the Taichung Blood Center. From the findings of this study, factors associated with adverse events related to blood donation include lower age, BMI, predonation SBP, and predonation DBP.

Table 6

Odds ratio and 95% confidence intervals in multivariate logistic regression analysis in the adverse events of the fixed donation sites.

Demographic characteristics	OR (95% CI)	P-value*
Overall		
Season		.735
Hot weather season (25.75 ± 4.47°C)	1.05 (0.79–1.39)	
Non-hot weather season (21.22 ± 4.96°C)	1.00	
Age, yr		<.001
<35	3.16 (2.29–4.36)	
≥35	1.00	
Gender, yr		.041
Male	1.00	
Female	1.51 (1.02–2.24)	
Donation status		
First-time	11.77 (7.31–18.96)	<.001
Repeat	1.00	
Donation volume, mL		<.001
500	2.82 (1.86–4.29)	
250	1.00	
Predonation SBP, mm Hg		0.754
<124	0.94 (0.65–1.52)	
≥124	1.00	
Predonation DBP, mm Hg		0.777
<75	1.06 (0.73–1.20)	
≥75	1.00	
BMI, kg/m ²		.126
<24	1.29 (0.93–1.77)	
≥24	1.00	

BMI = body mass index, CI = confidence interval, DBP = diastolic blood pressure, EBV = estimated blood volume, OR = odds ratio, SBP = systolic blood pressure.

* P-value from Chi-square test.

First-time donors might be more anxious and fearful than repeat donors as they have had no experience donating blood. Anxiety has direct emotional consequences that can lead to VVR.^[10] More experienced blood donors have less fear.^[11] Fear may be a predictor of adverse events.^[12,13] Almutairi et al^[14] also reported that first-time donors have a 2.2-fold increased risk of adverse events. Moreover, first-time donors with adverse reaction experience may be less likely to donate again.^[15]

Many studies have shown that female gender is associated with VVRs, highlighting the gender differences in incidences of adverse reactions.^[16] Gender differences in autonomic functions are associated with differences in BP. There are also gender differences in the renin angiotensin system and the effects of bound angiotensin II type 2 receptor on renal vascular resistance. Renal sympathetic nervous activity is the main cause of vascular resistance in the evaluation of BP in female subjects.^[17] In this study, we also found a higher risk of VVR among female donors than among male donors.

The results of our study also showed that blood donors less than 35 years old have higher risk of VVRs. Baroreflex sensitivity (BRS) is negatively correlated with age. In 1 study, BRS was found to be positively correlated with healthy, young females.^[18] Therefore, young blood donors have higher BRS than older blood donors. When blood donors experience physical or psychological stress, there is increased pulse rate or arterial pressure, leading to vagal stimulation, which produces bradycardia and hypotension. High BRS in young people can explain why younger blood donors are at higher risk of adverse events than older blood donors.

Table 7

Odds ratio and 95% confidence intervals in multivariate logistic regression analysis in the adverse events of the mobile donation sites.

Demographic characteristics	OR (95% CI)	P-value*
Overall		
Season		.753
Hot weather season (25.75 ± 4.47°C)	1.03 (0.88–1.19)	
Non-hot weather season (21.22 ± 4.96°C)	1.00	
Age, yr		<.001
<35	3.20 (2.70–3.79)	
≥35	1.00	
Gender, yr		<.001
Male	1.00	
Female	1.45 (1.19–1.75)	
Donation status		
First-time	5.77 (4.57–7.31)	<.001
Repeat	1.00	
Donation volume, mL		<.001
500	2.82 (1.86–4.29)	
250	1.00	
Predonation SBP, mm Hg		0.003
<124	1.33 (1.10–1.62)	
≥124	1.00	
Predonation DBP, mm Hg		0.970
<75	1.00 (0.83–1.20)	
≥75	1.00	
BMI, kg/m ²		.035
<24	1.21 (1.01–1.43)	
≥24	1.00	

BMI = body mass index, CI = confidence interval, DBP = diastolic blood pressure, EBV = estimated blood volume, OR = odds ratio, SBP = systolic blood pressure.

* P-value from Chi-square test.

In addition, blood donors who donated at mobile site had higher risk of VVR than those who donated at fixed site. The reasons may be less space and less relaxed environment at mobile sites. It is important to ensure that mobile sites have adequate ventilation and space for blood donors to rest for 10 to 15 minutes.

We also observed that BP and BMI are significantly associated with adverse events, consistent with the findings of previous studies. BMI and BP were lower in the adverse events group compared to the control group.^[6,19]

Our study showed a higher EBV in adverse events group than in control group. These results differed from the findings of a previous study.^[20] There are 3 possible reasons for this discrepancy. First, we excluded WB donors aged 17 to 19 years. EBV is associated with the risk of adverse events in this age group.^[21] Second, we considered different EBV formulas for males and females in this study. The cutoff points of EBV were the same for males and females, such that we did not consider the differences in EBV distributions between genders. Third, donation volume divided by EBV should be considered in adverse events.

To illustrate the joint effect of the 3 most significant factors, a multiple logistic regression model was used to assess the combinations of age, gender, and donation status. We found that the combined effects of any 2 or 3 factors result in stronger associations than any 1 factor alone.

Adverse events are thought to be caused by various physical (eg, standing up after donating blood) and psychological reasons (eg, pain, fear).^[4] Moreover, neurally mediated reflex, relative

Table 8**Joint effect of age, gender, and donation status on adverse events.**

Demographic characteristic	Adverse events n = 1255	No adverse event n = 5083	Total	OR (95% CI)	P-value
Overall					
Age (yr), gender, and donation status					
≥35, male and repeat	186	1686	1872	1.00	
<35, male and repeat	411	1201	1612	2.48 (2.27–3.40)	<.001
≥35, male and first-time	5	15	20	5.67 (1.71–18.79)	.005
≥35, female and repeat	95	1083	1178	3.08 (2.02–4.70)	<.001
<35, female and repeat	280	892	1172	9.34 (6.31–13.83)	<.001
<35, male and first-time	92	118	210	14.57 (19.36–115.72)	<.001
≥35, female and first-time	52	32	84	47.33 (19.36–115.72)	<.001
<35, female and first-time	128	62	190	100.57 (48.45–208.75)	<.001

CI = confidence interval, OR = odds ratio.

hypovolemia, posture change,^[22] and evaluated serum protein and Hb^[23] can lead to adverse events.

Aging of the population is a global challenge for blood services.^[24,25] Effective strategies for recruitment and retention of young, first-time blood donors are very important. Prevention of adverse events is also of importance to blood centers as blood donors who experience VVR are less likely to give blood again. Reducing adverse events improves donor retention.^[26] VVS is the most common adverse event among WB donors.^[8] VVS not only can cause injuries, but also decreases the return behavior of blood donors.^[27] Therefore, it is important to understand and prevent adverse events related to blood donation and to improve blood donation safety.

This study has several limitations. First, we did not include blood donors aged 17 to 19 in this study. Teenage blood donors have significant risk of adverse reactions and injuries after blood donation when compared with adults.^[28] The reason is that the Ethical Review Board of the Taiwan Blood Services Foundation requires subjects to be legal adults. Second, one of the criteria for blood donors was pulse rate of 60 to 100 beats per minute. Pulse rate is measured at blood centers, but this data is not recorded. Third, Hb screening for blood donors was based only on copper sulfate, meaning no quantitative Hb data. A previous study showed that higher Hb level is associated with adverse events for WB donations. Blood donors are healthy with normal cardiovascular and renal functions. They can manage a slightly negative balance in water normally, but not when it is due to blood loss. If there is a negative balance of water during blood donation, loss of intravascular volume may not be supported.^[14]

5. Conclusion and recommendation

In conclusion, younger (<35 years old), female, first-time donors and those with a donation volume of 500 mL, donation at mobile site, lower predonation SBP (<124 mm Hg) and lower BMI (<24 kg/m²) are at risk of adverse event. In addition, a novel finding of this study is that female first-time donors aged <35 years have 100.54 fold risk of adverse event when compared with male repeat donors aged ≥35 years.

Moreover, drinking 500 mL of water or isotonic drink before donation is useful for preventing adverse reactions in blood donors.^[22] At blood donation sites of the Taichung Blood Center, blood donors are suggested to drink water before phlebotomy to promote better intravascular volume.

After controlling for other important demographic and health factors, VVRs are more likely to occur among fearful blood

donors.^[29] First-time donors might be more anxious and fearful than repeat donors. At Taichung Blood Center donation sites, first-time donors are given a silicone bracelet to wear before phlebotomy. This bracelet reminds staff members to pay more attention to them. They explain the process and chat with donors to divert their attention and reduce psychological stress. Providing a comfortable and friendly environment for donors is important.

Based on the results of this study, we can educate staff at donation sites regarding risk factors and identification of those at risk to prevent adverse events. The collection staff should be well trained in collecting techniques to minimize adverse reactions such as nerve injury or pain.

Further, if appropriate interventions^[30,31] such as practicing applied muscle tension for increasing BP are carried out, we speculate that incidences of adverse reactions can be reduced.

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References

- [1] Sheldon RS, Grubb BP, Olshansky B, et al. 2015 Heart rhythm society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. *Heart Rhythm* 2015;12:e41–63.
- [2] Ministry of Health Labour and Welfare. Annual Report of Blood Programme. 2011 (Japan)
- [3] Gilchrist PT, Ditto B. Sense of impending doom: inhibitory activity in waiting blood donors who subsequently experience vasovagal symptoms. *Biol Psychol* 2015;104:28–34.
- [4] Gilchrist PT, McGovern GE, Bekkouche N, et al. The vasovagal response during confrontation with blood-injury-injection stimuli: the role of perceived control. *J Anxiety Disord* 2015;31:43–8.
- [5] Aardal Eriksson E, Mobäck C, Jakobsson S, et al. Iron depletion in blood donors – have extended erythrocyte and reticulocyte parameters diagnostic utility? *Transfus Apher Sci* 2015;53:76–81.

- [6] Takanashi M, Odajima T, Aota S, et al. Risk factor analysis of vasovagal reaction from blood donation. *Transfus Apher Sci* 2012;47:319–25.
- [7] Thijsen A, Masser B. Vasovagal reactions in blood donors: risks, prevention and management. *Transfus Med* 2017;29(S1):1322.
- [8] Bravo M, Kamel H, Custer B, et al. Factors associated with fainting: before, during and after whole blood donation. *Vox Sang* 2011;101:303–12.
- [9] Narbey D, Fillet AM, Jbilou S, et al. Case-control study of immediate and delayed vasovagal reactions in blood donors. *Vox Sang* 2016;111:257–65.
- [10] Viar MA, Etzel EN, Ciesielski BG, et al. Disgust, anxiety, and vasovagal syncope sensations: a comparison of injection-fearful and nonfearful blood donors. *J Anxiety Disord* 2010;24:941–5.
- [11] France CR, France JL. Fear of donation-related stimuli is reported across different levels of donation experience. *Transfusion* 2018;58:113–20.
- [12] France CR, France JL, Himawan LK, et al. How afraid are you of having blood drawn from your arm? A simple fear question predicts vasovagal reactions without causing them among high school donors. *Transfusion* 2013;53:315–21.
- [13] France CR, France JL, Kowalsky JM, et al. Assessment of donor fear enhances prediction of presyncopal symptoms among volunteer blood donors. *Transfusion* 2012;52:375–80.
- [14] Almutairi H, Salam M, Alajlan A, et al. Incidence, predictors and severity of adverse events among whole blood donors. *PLoS One* 2017;12:e0179831.
- [15] Masser BM, White KM, Terry DJ. Beliefs underlying the intention to donate again among first-time blood donors who experience a mild adverse event. *Transfus Apher Sci* 2013;49:278–84.
- [16] Garozzo G, Crocco I, Giussani B, et al. Adverse reactions to blood donations: the READ project. *Blood Transfus* 2010;8:49–62.
- [17] Leete J, Layton AT. Sex-specific long-term blood pressure regulation: modeling and analysis. *Comput Biol Med* 2019;104:139–48.
- [18] Taylor CE, Witter T, El Sayed K, et al. Relationship between spontaneous sympathetic baroreflex sensitivity and cardiac baroreflex sensitivity in healthy young individuals. *Physiol Rep* 2015;3:e12536.
- [19] Thijsen A, Masser B. Vasovagal reactions in blood donors: risks, prevention and management. *Transfus Med* 2019;29(Suppl 1):13–22.
- [20] Gonzalez TT, Sabino EC, Schlumpf KS, et al. Vasovagal reactions in whole blood donors at three REDS-II blood centers in Brazil. *Transfusion* 2012;52:1070–8.
- [21] Rios JA, Fang J, Tu Y, et al. The potential impact of selective donor deferrals based on estimated blood volume on vasovagal reactions and donor deferral rates. *Transfusion* 2010;50:1265–75.
- [22] Morand C, Coudurier N, Rolland C, et al. Prevention of syncopal-type reactions after whole blood donation: a cluster-randomized trial assessing hydration and muscle tension exercise. *Transfusion* 2016;56:2412–21.
- [23] Odajima T, Takanashi M, Sugimori H, et al. Impact of elevated hemoglobin and serum protein on vasovagal reaction from blood donation. *PLoS One* 2016;11:e0148854.
- [24] Katalinic A, Peters E, Beske F, et al. Projection of morbidity 2030 and 2050: impact for the national health system and blood supply. *Transfus Med Hemother* 2010;37:155–9.
- [25] Johannsdottir V, Gudmundsson S, Moller E, et al. Blood donors in Iceland: a nationwide population-based study from 2005 to 2013. *Transfusion* 2016;56:1654–61.
- [26] Custer B, Rios JA, Schlumpf K, et al. Adverse reactions and other factors that impact subsequent blood donation visits. *Transfusion* 2012;52:118–26.
- [27] Eder AF, Notari EP, Dodd RY. Do reactions after whole blood donation predict syncope on return donation? *Transfusion* 2012;52:2570–6.
- [28] Eder AF, Hillyer CD, Dy BA, et al. Adverse reactions to allogeneic whole blood donation by 16- and 17-year-olds. *JAMA* 2008;299:2279–86.
- [29] France CR, France JL, Conatser R, et al. Predonation fears identify young donors at risk for vasovagal reactions. *Transfusion* 2019;59:2870–5.
- [30] Thijsen A, Gemelli CN, Davison TE, et al. Does using applied muscle tension at strategic time points during donation reduce phlebotomist- and donor-reported vasovagal reaction rates? A three-armed randomized controlled trial. *Transfusion* 2018;58:2352–9.
- [31] Thijsen A, Fisher J, Gemelli CN, et al. Facilitating donor compliance with strategies to prevent vasovagal reactions: comparison of web-based and in-center approaches. *Transfusion* 2017;57:2449–57.