Adverse factors responsible for below-normal platelet count after laparoscopic splenectomy and azygoportal disconnection

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ABSTRACT

Background/Aims: Splenectomy is regarded as an effective curative treatment for thrombocytopenia caused by hypersplenism in patients with cirrhosis. However, in clinical practice, thrombocytopenia is not resolved by splenectomy in all patients. This study aimed to evaluate the adverse factors responsible for platelet (PLT) counts below the normal lower limit following laparoscopic splenectomy and azygoportal disconnection (LSD).

Materials and Methods: We retrospectively evaluated the outcomes of 123 cirrhotic patients with portal hypertensive bleeding and secondary hypersplenism, who underwent LSD and who had PLT counts <125×109/L (non-normal group) or ≥125×109/L (normal group) at the postoperative month (POM) 3, between April 2014 and March 2017.

Results: Sixteen patients (13.01%) had PLT counts <125×109/L at POM 3 after LSD, while the remaining 107 patients had normal counts. We analyzed 25 perioperative variables in both groups. A logistic multivariate regression identified age (relative risk [RR] 1.082, 95% confidence interval [CI] 1.018-1.150) and longitudinal spleen diameter (RR 0.977, 95% CI 0.955-1.000) as significant independent factors for the PLT count <125×109/L at POM 3. Bivariate correlation analysis showed that age >50 years and longitudinal spleen diameter ≤160 mm were threshold values for an increased risk of the PLT count <125×109/L at POM 3 after LSD.

Conclusion: Age was an independent positive predictor and longitudinal spleen diameter an independent negative predictor of PLT count <125×109/L at POM 3 after LSD.

Keywords: Platelet, splenectomy, laparoscopy, cirrhosis, portal hypertension

INTRODUCTION

The high incidences of chronic hepatitis B and C virus infections worldwide are associated with increased incidences of hypersplenism, with splenomegaly secondary to cirrhotic portal hypertension. Splenectomy is regarded as a first-line curative treatment for thrombocytopenia and leukopenia resulting from hypersplenism in patients with cirrhosis. It also has been shown to improve coagulation and liver function, and it plays an important role in the surgical strategy for hepatocellular carcinoma by alleviating thrombocytopenia in cirrhotic patients (1-5). Furthermore, the Hassab procedure (splenectomy and azygoportal disconnection) is a common treatment strategy for patients suffering from hypersplenism together with esophagogastric variceal bleeding in Asia.

Splenectomy is always followed by increased blood viscosity as a result of high platelet (PLT) and leukocyte counts secondary to the absence of splenic breakdown. Previous studies reported that the mean postoperative PLT count usually increased to 231-399×10^9/L after splenectomy or the Hassab procedure (6-8), which was within normal limits. However, thrombocytopenia is not resolved by splenectomy in all patients in clinical practice; some patients maintain a postoperative PLT count below the normal lower limit (125×10^9/L) despite splenectomy, suggesting that this procedure may not be suitable in all cases. This may result in patient dissatisfaction, and even medical violence, in some countries (9,10). It is therefore necessary to determine the factors responsible for this treatment failure and to identify those patients at risk of maintaining a low postoperative PLT. We aimed to identify the adverse factors associated with a PLT count below the normal lower limit after splenectomy. We conducted a retrospective study to compare the demographic, preoperative, and intraoperative characteristics between pa-

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tients with PLT counts ≥125×10⁹/L and those with counts <125×10⁹/L at postoperative month (POM) 3 after laparoscopic splenectomy and azygoportal disconnection (LSD) for portal hypertensive bleeding and secondary hypersplenism.

MATERIALS AND METHODS

Patients

Patients were included in the study if they met the following criteria: diagnosed with cirrhosis of any etiology; aged 18-80 years; had a history of esophageal/gastric variceal bleeding and secondary hypersplenism; liver function Child-Pugh A or B; hypersplenism with a PLT count <100×10⁹/L; no portal vein system thrombosis proved by ultrasonographic evaluation on admission; underwent LSD; and completed a 3-month follow-up.

Patients were excluded for the following reasons: any malignancy; hypercoagulable state not resulting from liver disease; management with oral contraceptives, anticoagulation agents, or antiplatelet agents; uncontrolled hypertension or peptic ulcer disease; hemorrhagic stroke; or human immunodeficiency virus infection.

A total of 123 patients satisfied the inclusion criteria between April 2014 and March 2017, and they were diagnosed with esophageal/gastric variceal bleeding and secondary hypersplenism due to cirrhotic portal hypertension in our department. All the patients underwent LSD. All operations were performed by the same experienced surgical team. The LSD procedure was carried out as described previously (11,12). The clinical characteristics of the patients were analyzed retrospectively. This study was approved by the Ethics Committee of our institution. Written informed consent was provided by each patient. The methods were performed in accordance with the relevant guidelines and regulations.

Clinical data were collected retrospectively. Preoperative patient data included age, gender, etiology of cirrhosis, hypertension, diabetes mellitus, Child-Pugh classification, the longitudinal spleen diameter, the main portal vein diameter, spleneolus, hemoglobin levels, the PLT count, prothrombin time, and levels of total bilirubin, plasma albumin, alanine aminotransferase, blood urea nitrogen, creatinine, laminin, precollagen III, collagen IV, and hyaluronidase. Intraoperative data included the operation time, intraoperative blood loss, and intraoperative blood transfused. Postoperative data included the PLT count on postoperative days (POD) 7 and 10, and at POM 1 and 3. Patients with a PLT count at POM 3 below the normal lower limit (125×10⁹/L) were classified as the non-normal group (n=16) and those with a PLT count ≥125×10⁹/L were placed in the normal group (n=107).

Statistical analysis

All statistical analyses were performed using the SPSS 22.0 software (IBM Corp.; Armonk, NY, USA). p values <0.05 were considered statistically significant. Data are presented as mean (standard deviation), median (range), or percentage. Group means were compared using Student's *t*-tests or Mann-Whitney U tests, as appropriate. Percentages were compared using χ^2 tests. Bivariate correlation was used to determine the significance levels of patient age and longitudinal spleen diameter. Multivariate regression analysis was performed with forward stepwise elimination of nonsignificant variables.

RESULTS

Baseline patient characteristics

The non-normal group included 16 (13.01%) patients (6 males, 10 females; mean age, 60.8±8.2 years; range, 44-73 years) with portal hypertensive bleeding and secondary hypersplenism due to liver cirrhosis. These patients had been admitted because of variceal bleeding. All 16 patients suffered from splenomegaly, with a longitudinal spleen diameter of 99-207 mm. The non-normal group included the remaining 107 (86.99%) patients (72 males, 35 females, mean age, 52.0±10.2 years; range, 21-77) with PLT counts ≥125×10⁹/L at POM 3. These patients were also admitted because of variceal bleeding and had spleen diameters of 132-300 mm.

Adverse factors responsible for below-normal platelet count

The 25 analyzed variables in the non-normal and normal groups are shown in Table 1. The variables shown to differ significantly between the two groups were gender, age, and longitudinal spleen diameter. These significant variables were regarded as independent variables, and PLT count <125×10⁹/L at POM 3 as a dependent variable. Multivariate logistic regression identified age (relative risk [RR] 1.082, 95% confidence interval [CI] 1.018-1.150) and longitudinal spleen diameter (RR 0.977, 95% CI 0.955-1.000) as significant variables affecting the risk of PLT count <125×10⁹/L at POM 3 (Table 2).

Postoperative PLT count changes with time

The mean PLT count changes from admission to POM 3 fluctuated widely (p<0.001; Figure 1), with the peak

Table 1. Demographic, preoperative, and intraoperative characteristics of patients with platelet counts ≥ or <125×10⁹/L at the postoperative month 3

Variable	Non-normal (n=16)	Normal (n=107)	p
Sex (female/male)	10/6	35/72	0.021
Age (years)	60.8±8.2	52.0±10.2	0.001
Etiology[a]	11/1/1/1/1/1	72/7/4/3/9/12	0.957
Hypertension	3	15	0.904
Diabetes mellitus	3	16	0.983
Child-Pugh classification (A/B)	10/6	60/47	0.628
WBC ($\times10^9$/L)	3.17±1.87	3.00±2.43	0.779
Hb (g/L)	109.1±17.4	103.1±28.2	0.250
PLT ($\times10^9$/L)	40.2±17.1	46.7±14.7	0.110
PT (s)	15.93±1.59	16.29±1.96	0.484
TBIL (μmol/L)	23.74±9.87	22.50±11.82	0.692
ALB (g/L)	37.13±4.47	39.14±6.15	0.213
ALT (U/L)	30.3±21.2	27.7±16.6	0.586
BUN (mmol/L)	6.03±2.21	5.65±2.11	0.507
Cr (μmol/L)	73.12±19.32	73.78±20.36	0.903
Spleneolus	0	4	0.975
Longitudinal spleen diameter (mm)	165.1±29.7	184.8±27.8	0.010
Main portal vein diameter (mm)	13.3±2.8	14.3±2.5	0.112
Laminin (μg/L)	46.06 (9.39-1000)	46.88 (2.0-1000)	0.682
Precollagen III (μg/L)	61.28±39.86	52.32±28.48	0.270
Collagen IV (μg/L)	55.98±30.21	57.71±34.02	0.847
Hyaluronidase (μg/L)	189.18±131.49	165.95±159.43	0.580
Operation time (min)	162.8±48.0	174.8±42.4	0.303
Estimated blood loss (mL)	114.4±123.6	159.3±249.1	0.481
No. of blood transfusions	1	3	>0.99

Data are given as mean±standard deviation, median (range), or number of patients, as indicated. WBC: white blood cells; Hb: hemoglobin; PLT: platelets; PT: prothrombin time; TBIL: total bilirubin; ALB: albumin; ALT: alanine aminotransferase; BUN: blood urea nitrogen; Cr: creatinine

[a]Hepatitis B/hepatitis C/schistosomiasis/alcohol/autoimmunity/idiopathic cirrhosis

mean PLT count occurring on POD 10. The mean PLT count on POD 10 (383.5±186.9×10⁹/L) was significantly higher than on POD 7 (271.1±135.6×10⁹/L), POM 1 (276.1±154.5×10⁹/L), or POM 3 (245.9±115.0×10⁹/L) (all $p<0.001$). There was no significant difference in the mean PLT count between POM 1 and POM 3 ($p>0.05$).

Association between age, longitudinal spleen diameter, and PLT count <125×10⁹/L at POM 3

Bivariate correlation analysis was performed to analyses the relationship between these significant variables and the occurrence of a PLT count <125×10⁹/L at POM 3. The variables were age and longitudinal spleen diameter. Age and longitudinal spleen diameter were divided into groups. According to the correlation coefficient, the threshold values for a PLT count <125×10⁹/L were age >50 years (Table 3) and longitudinal spleen diameter ≤160 mm (Table 4).

Patients were divided into the following age groups: 21-35 years, 36-50 years, 51-65 years, and 66-80 years. The PLT count at POM 3 decreased gradually with increasing

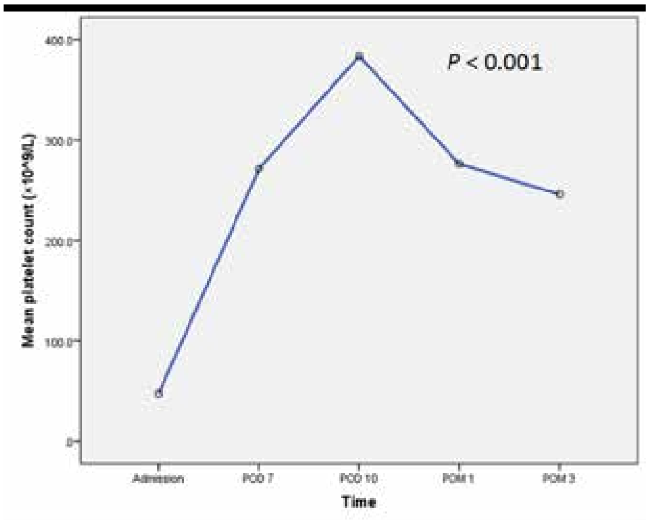

Figure 1. Changes in mean platelet counts
POD: postoperative day; POM: postoperative month

Table 2. Multivariate logistic regression analysis

Independent variables	B	SE	Wald	df	Sig	Exp (B)	95%CI
Age	0.079	0.031	6.383	1	0.012	1.082	1.018-1.150
Longitudinal spleen diameter	-0.023	0.012	3.713	1	0.054	0.977	0.955-1.000

SE: standard error; CI: confidence interval age, as shown in Table 5. The overall difference among these measures were significant (p=0.004; Table 5; Figure 2). The incidences of a PLT count <125×10⁹/L at POM 3 increased gradually with increasing age as shown in Table 5. The overall differences among these incidences were significant (p=0.001; Table 5).

Table 3. Bivariate correlation analysis of the relationship between age and platelet count <125×10⁹/L at the postoperative month 3

Correlation Factor	Correlation Coefficient	p
Age (years)		
>45	-0.152	0.093
>50	-0.251	0.005
>55	-0.270	0.002
>60	-0.266	0.003
>65	-0.225	0.012

Table 4. Bivariate correlation analysis of the relationship between longitudinal spleen diameter and the platelet count <125×10⁹/L at the postoperative month 3

Correlation Factor	Correlation Coefficient	p
Longitudinal spleen diameter (mm)		
>170	0.158	0.081
>165	0.176	0.051
>160	0.231	0.010
>155	0.182	0.044
>150	0.166	0.067

Similarly, all patients (except 1 with a spleen diameter of 99 mm) were divided into groups according to longitudinal spleen diameter as follows: 121-160 mm, 161-200 mm, and ≥201 mm groups. The PLT count at POM 3 increased gradually with increasing spleen diameter as shown in Table 6. The overall comparison of these measures was significant (*P*=0.003; Table 6, Figure 3). The incidences of a PLT count <125×10⁹/L on POM 3 decreased gradually with increasing spleen diameter, as shown in Table 6. The overall comparison of these incidences was significant (*P*=0.016; Table 6).

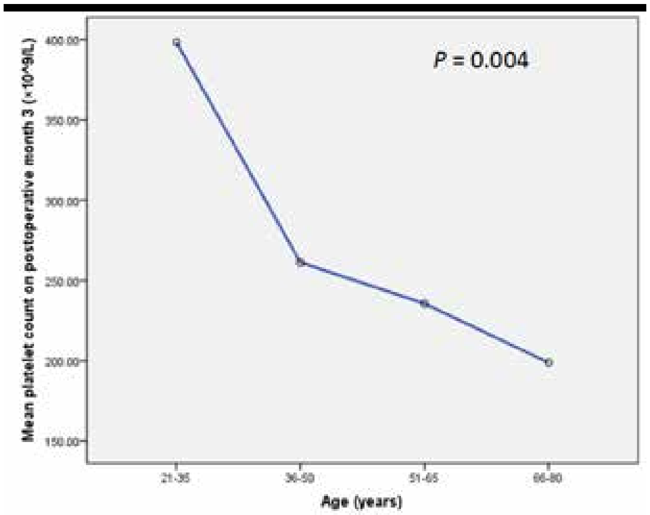

Figure 2. Changes in mean platelet counts at the postoperative month 3 in different age groups

Table 5. Changes in the platelet count at the postoperative month 3 in different age groups

	21-35 years	36-50 years	51-65 years	66-80 years	21-80 years	p (Total)
n	3	52	53	15	123	
PLT count (×10⁹/L)	398.3±94.4	261.2±117.9	235.6±104.8	198.8±117.9	245.9±115.0	0.004
No. with PLT count <125 (×10⁹/L)	0 (0.0%)	2 (3.8%)	9 (17.0%)	5 (33.3%)	16 (13.0%)	0.001

Data are given as mean±standard deviation, or number (percentage) of patients, as indicated
PLT: platelets

Table 6. Changes in the platelet count at the postoperative month 3 in patients with different longitudinal spleen diameters

	121-160 mm	161-200 mm	≥201 mm	≥121 mm	p (Total)
n	29	63	30	122	
PLT count (×10⁹/L)	188.9±78.5	260.2±122.4	275.5±111.3	247.0±114.8	0.003
No. with PLT count <125 (×10⁹/L)	7 (24.1%)	7 (11.1%)	1 (3.3%)	15 (12.3%)	0.016

Data are given as mean±standard deviation, or number (percentage) of patients, as indicated PLT: platelets

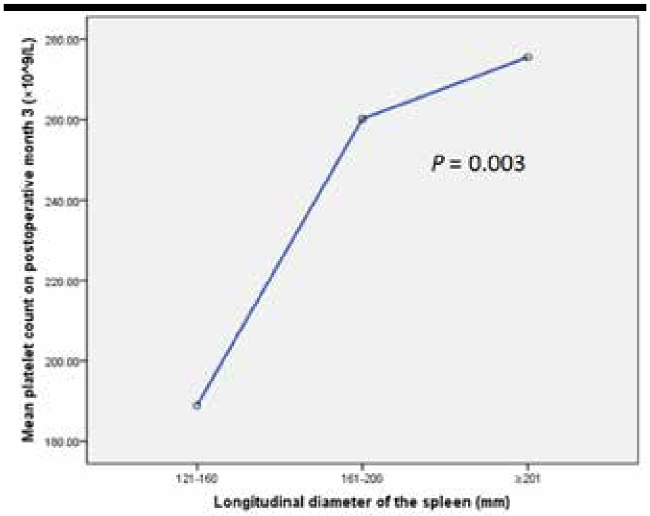

Figure 3. Changes in mean platelet counts at the postoperative month 3 in patients with different longitudinal spleen diameters

DISCUSSION

Platelet counts are known to decrease progressively with age in the general population (13-16), with a mean decrease of 6-9×10⁹/L with every additional 10 years of aging (15,16). However, the reasons for this age-related effect are presently unexplained. The decrease in the PLT count during aging may reflect a reduced hematopoietic stem cell reserve or decreased proliferation and differentiation capabilities of hematopoietic stem cells in older people. However, further investigations are required to explore the mechanisms underlying these age-related changes.

The above hypotheses may at least partly explain why age was an independent risk factor for PLT count <125×10^9/L at POM 3 after LSD in the present study. Furthermore, a bivariate correlation analysis also identified age >50 years as a threshold value for an increased risk of a lower PLT count and a PLT count <125×10^9/L at POM 3. Consistently, the mean PLT counts at POM 3 in patients aged 51-65 and 66-80 years were lower than those in patients aged 21-35 and 36-50 years, and below the total mean PLT count at POM 3. In addition, PLT counts <125×10^9/L at POM 3 were more frequent in patients aged 51-65 and 66-80 years compared with patients aged 21-35 and 36-50 years, and more frequent than the total mean incidence of PLT count <125×10^9/L at POM 3.

The spleen is an immune-system center containing large numbers of lymphocytes and macrophages, with bigger spleens having more macrophages. Thrombocytopenia is known to result from hypersplenism due to excessive phagocytosis of macrophages that engulf PLTs, and a larger spleen thus leads to increased phagocytosis and fewer PLTs. Removal of the enlarged spleen should thus allow PLT numbers to recover, and postoperative PLT numbers may be positively associated with the spleen size. Smaller spleen may be more inclined to have a lower PLT count after LSD. Accordingly, the current study found that longitudinal spleen diameter was an independent positive predictor of the PLT count <125×10^9/L at POM 3.

A bivariate correlation analysis in the present study also revealed that the longitudinal spleen diameter ≤160 mm was a threshold value, below which patients were more likely to have a lower PLT count and a higher risk of a PLT count <125×10^9/L at POM 3. Consistently, the mean PLT count at POM 3 in patients with a spleen diameter of 121-160 mm was lower than that in patients with diameters of 161-200 and ≥201 mm, and lower than the total mean PLT count at POM 3. Furthermore, the incidence of a PLT count <125×10^9/L at POM 3 was higher among patients with spleen diameters of 121-160 mm compared with those with diameters of 161-200 and ≥201 mm, and higher than the total mean incidence of the PLT count <125×10^9/L at POM 3.

In the present study, 5 of the 21 (23.8%) patients with a PLT count <125×10^9/L at POM 3 were aged age >50 years and had a longitudinal spleen diameter ≤160 mm. This suggests that patients older than 50 years who also have a longitudinal spleen diameter ≤160 mm may be at increased risk of having a PLT count <125×10^9/L at POM 3 after LSD.

It is necessary to warn patients preoperatively of the possibility of having a PLT count below the normal lower limit after surgery, especially in the case of patients older than 50 years and/or those with a longitudinal spleen diameter ≤160 mm, to avoid postoperative patient dissatisfaction (17).

This retrospective observational study showed that age is an independent positive predictor, and longitudinal spleen diameter is an independent negative predictor of having a PLT below the normal lower limit after LSD. This study also identified age >50 years and a longitudinal spleen diameter ≤160 mm as threshold values for increased risks of a lower PLT count and a PLT count below the normal lower limit at POM 3 after LSD. This study may be limited by its small sample size. Prospective trials with a large sample size are required to confirm these findings.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki “Ethical Principles for Medical Research Involving Human Subjects” (amended in October 2013).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer review.

Author Contributions: Concept - D.S.B., G.Q.J., W.Y.S.; Design - D.S.B., G.Q.J., W.Y.S.; Supervision - D.S.B., G.Q.J.; Materials - D.S.B., W.Y.S., S.J.J., P.C., G.Q.J.; Data Collection and/or Processing - S.J.J., P.C., C.Z.; Analysis and/or Interpretation - S.J.J., P.C., G.Q.J.; Literature Search - G.Q.J., W.Y.Z., C.Z.; Writing Manuscript - D.S.B., G.Q.J., W.Y.S.; Critical Reviews - G.Q.J., D.S.B.

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REFERENCES

1. Ikegami T, Shimada M, Imura S. Recent role of splenectomy in chronic hepatic disorders. Hepatol Res 2008; 38: 1159-71. [CrossRef]

2. Imura S, Shimada M, Utsunomiya T, et al. Impact of splenectomy in patients with liver cirrhosis: results from 18 patients in a single center experience. Hepatol Res 2010; 40: 894-900. [CrossRef]

3. Tomikawa M, Hashizume M, Akahoshi T, et al. Effects of splenectomy on liver volume and prognosis of cirrhosis in patients with esophageal varices. J Gastroenterol Hepatol 2002; 17: 77-80. [CrossRef]

4. Ushitora Y, Tashiro H, Takahashi S, et al. Splenectomy in chronic hepatic disorders: portal vein thrombosis and improvement of liver function. Digest Surg 2011; 28: 9-14. [CrossRef]

5. Shimada M, Hashizume M, Shirabe K, Takenaka K Sugimachi K. A new surgical strategy for cirrhotic patients with hepatocellular carcinoma and hypersplenism. Performing a hepatectomy after a laparoscopic splenectomy. Surg Endosc 2000; 14: 127-130. [CrossRef]

6. Bao H, He Q, Dai N, Ye R, Zhang Q. Retrospective Study to Compare Selective Decongestive Devascularization and Gastrosplenic Shunt versus Splenectomy with Pericardial Devascularization for the Treatment of Patients with Esophagogastric Varices Due to Cirrhotic Portal Hypertension. Med Sci Monit 2017; 23: 2788-95. [CrossRef]

7. Qian YY, Li K. The early prevention and treatment of PVST after laparoscopic splenectomy: A prospective cohort study of 130 patients. Int J Surg 2017; 44: 147-51. [CrossRef]

8. Su AP, Zhang ZD, Tian BL, Zhu JQ. Transjugular intrahepatic portosystemic shunt versus open splenectomy and esophagogastric devascularization for portal hypertension with recurrent variceal bleeding. Hepatobiliary Pancreat Dis Int 2017; 16: 169-75. [CrossRef]

9. Jiang Y, Ying X, Kane S, Mukhopadhyay M, Qian X. Violence against doctors in China. Lancet 2014; 384: 744-5. [CrossRef]

10. Bawaskar HS. Violence against doctors in India. Lancet 2014; 384: 955-6. [CrossRef]

11. Bai DS, Qian JJ, Chen P, et al. Modified laparoscopic and open splenectomy and azygoportal disconnection for portal hypertension. Surg Endosc 2014; 28: 257-64. [CrossRef]

12. Jiang G, Qian J, Yao J, Wang X, Jin S, Bai D. A New Technique for Laparoscopic Splenectomy and Azygoportal Disconnection. Surg Innov 2014; 21: 256-62. [CrossRef]

13. Vázquez-Santiago M, Ziyatdinov A, Pujol-Moix N, et al. Age and gender effects on 15 platelet phenotypes in a Spanish population. Comput Biol Med 2016; 69: 226-33. [CrossRef]

14. Biino G, Santimone I, Minelli C, et al. Age- and sex-related variations in platelet count in Italy: a proposal of reference ranges based on 40987 subjects' data. PLoS One 2013; 8: e54289. [CrossRef]

15. Biino G, Gasparini P, D'Adamo P, et al. Influence of age, sex and ethnicity on platelet count in five Italian geographic isolates: mild thrombocytopenia may be physiological. Br J Haematol 2012; 157: 384-7. [CrossRef]

16. Biino G, Balduini CL, Casula L, et al. Analysis of 12,517 inhabitants of a Sardinian geographic isolate reveals that predispositions to thrombocytopenia and thrombocytosis are inherited traits. Haematologica 2011; 96: 96-101. [CrossRef]

17. Wang XQ, Wang XT, Zheng JJ. How to end violence against doctors in China. Lancet 2012; 380: 647-8. [CrossRef]