Vascular Health and Risk Management

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ORIGINAL RESEARCH

Association of Clopidogrel with Interstitial Lung Disease: Gaining Insight Through the Japanese Pharmacovigilance Database

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Background: The P2Y12 receptor inhibitors clopidogrel and prasugrel are widely used. Clopidogrel and prasugrel have different metabolic pathways, but whether their adverse event (AE) profiles differ significantly is unclear.

Objective: This study aimed to compare the possible AEs induced by clopidogrel and prasugrel and to assess the rank-order of their AEs submitted to a spontaneous reporting database.

Materials and Methods: Data were extracted from the Japanese Adverse Drug Event Report database (JADER). Reports of AEs associated with clopidogrel and prasugrel were analyzed to calculate the reporting odds ratios (RORs) and 95% confidence intervals (CIs).

Results: Based on 5869 reports for clopidogrel (69.6%, men) and 513 reports for prasugrel (74.1%, men), 703 and 135 different AEs were identified, respectively. Bleeding complications including hemorrhage were commonly reported for both clopidogrel and prasugrel. As for AEs related to clopidogrel, unexpected AEs such as interstitial lung disease (227 reports; ROR, 1.77; 95% CI, 1.49–2.10), abnormal hepatic function (137 reports; ROR, 1.27; 95% CI, 1.07–1.51), and hepatocellular injury (96 reports; ROR, 120.0; 95% CI, 94.9–151.8) ranked at relatively high positions based on the number of occurrences, unlike prasugrel.

Conclusion: This analysis of the national pharmacovigilance database highlights distinct AE profiles for clopidogrel and prasugrel. Unexpected AEs associated with clopidogrel were identified, providing valuable insights for clinical monitoring and patient safety.

Keywords: P2Y12 platelet inhibitor, pharmacovigilance, adverse events, reporting odds ratio, signal detection, spontaneous reporting system

Introduction

Atherosclerotic arterial disease is one of the most frequent causes of death globally. Antithrombotic treatment with aspirin plus a P2Y12 receptor inhibitor is an integral part of management of patients with atherosclerotic cardiovascular and cerebrovascular disease and those with acute coronary syndrome (ACS) after percutaneous coronary intervention (PCI). Clopidogrel has been a traditional choice for P2Y12 inhibition; however, it shows significant interindividual variability in therapeutic outcomes.[1] Clopidogrel is a prodrug that requires bioactivation into its active metabolite via cytochrome P450 (CYP) 2C19.[2] The polymorphism driven by the metabolic activity of CYP2C19 significantly affects the pharmacokinetics of clopidogrel by altering its metabolic conversion, which in turn indirectly affects its therapeutic effects.[3] The prevalence of individuals with *CYP2C19* loss-of-function variants is more common in Asian patients. In contrast, prasugrel, a newer thienopyridine P2Y12 inhibitor, offers more consistent antiplatelet effects[4] and is less dependent on CYP enzymes for activation.[5] Considering these pharmacokinetic differences between clopidogrel and prasugrel, concerns have been raised regarding the adverse events (AEs) of these drugs, but little is known about them.

There is widespread acceptance that pharmacovigilance activities, which can detect unexpected post-marketing issues, are important for guaranteeing the safe use of drugs.[6,7] Notably, the analysis of pharmacovigilance data offers

Received: 13 July 2024
Accepted: 27 August 2024
Published: 2 September 2024

updated AE information to healthcare professionals and their patients, thereby reducing the overall risks of drugs. Certainly, drugs are approved for clinical use based on evidence of a satisfactory balance between potential benefits and risks. However, the safety profiles of drugs can change over time as their use expands, with changes in patients' characteristics, and with an increase in the number of patients exposed. In Japan, AEs are spontaneously reported by doctors, medical staff, patients, and pharmaceutical companies to the Pharmaceuticals and Medical Devices Agency (PMDA), which publicly releases them as the Japanese Adverse Drug Event Report (JADER) database.

The objective of this study was to compare the AE profiles of clopidogrel and prasugrel based on the JADER database.

Methods

AE reports in the JADER database can be freely downloaded from the PMDA website (http://www.pmda.go.jp/safety/info-services/drugs/adr-info/suspected-adr/0003.html) since April 1, 2004. This database includes only de-identified data; therefore, this study was deemed exempt from institutional review by the ethics committee of Osaka Medical and Pharmaceutical University. A total of 378,533 cases of data from the JADER database between April 2004 and January 2017 were examined.

Details of this database have been described previously.[8–15] In this study, only cases that were classified as "suspected medicine", because the drug itself could have been associated with the AEs, were extracted. For the AEs, the PT Names coded in MedDRA (version 23.0) were used. A cross-tabulation table was compiled based on two classifications: the presence or absence of a particular AE, and the presence or absence of the suspected medicine. Then, the reporting odds ratio (ROR), which is the number of reports of a specific AE caused by a drug divided by that of all other drugs in the database, was calculated. A signal is considered to be present when the lower limit of the 95% confidence interval (CI) of the ROR is greater than one.

All analyses were performed with SPSS for Windows software (ver. 19.0; SPSS Inc., Tokyo, Japan).

Results

During the study period, a total of 1,904,433 AE reports with both age and sex information were obtained. Of them, 5869 AE reports were associated with clopidogrel and 513 with prasugrel. Table 1 shows the patients' demographic information. AEs were frequently reported in men (clopidogrel, 69.6%; prasugrel, 74.1%) and in patients in their 70s (clopidogrel, 42.0%; prasugrel, 33.5%). Of note, the rate of recovery from AEs (clopidogrel, 39.2%; prasugrel, 41.9%) was high, followed by remission (clopidogrel, 24.6%; prasugrel, 27.7%).

Table 1 Characteristics of Study Patients

Variable	Clopidogrel (N = 5869)	Prasugrel (N = 513)
Sex		
Men, n (%)	4085 (69.6)	380 (74.1)
Women, n (%)	1784 (30.4)	133 (25.9)
Age		
10s, n (%)	1 (0.0)	0 (0.0)
20s, n (%)	8 (0.1)	3 (0.6)
30s, n (%)	19 (0.3)	0 (0.0)
40s, n (%)	129 (2.2)	7 (1.4)
50s, n (%)	516 (8.8)	37 (7.2)
60s, n (%)	1304 (22.2)	106 (20.7)
70s, n (%)	2466 (42.0)	172 (33.5)
80s, n (%)	1306 (22.3)	172 (33.5)
90≥, n (%)	120 (2.1)	16 (3.1)

(*Continued*)

Table 1 (Continued).

Variable	Clopidogrel (N = 5869)	Prasugrel (N = 513)
Reasons for use		
Cerebral infarction	931 (15.9)	1 (0.2)
Angina pectoris	510 (8.7)	57 (11.1)
Acute myocardial infarction	472 (8.0)	69 (13.5)
Angina unstable	322 (5.5)	33 (6.4)
Myocardial infarction	234 (4.0)	34 (6.6)
Antiplatelet therapy	207 (3.5)	6 (1.2)
Thrombosis prophylaxis	189 (3.2)	9 (1.8)
Lacunar infarction	175 (3.0)	0 (0.0)
Ischaemic cerebral infarction	130 (2.2)	0 (0.0)
Unknown/Others	2699 (46.0)	304 (59.2)
Outcome		
Recovery, n (%)	2298 (39.2)	215 (41.9)
Remission, n (%)	1444 (24.6)	142 (27.7)
After affects, n (%)	158 (2.7)	41 (8.0)
No recovery, n (%)	372 (6.3)	60 (11.7)
Death, n (%)	505 (8.6)	38 (7.4)
Unknown, n (%)	1092 (18.6)	17 (3.3)

In the analysis, 703 and 135 different AEs identified the "suspected medicine" as clopidogrel and prasugrel, respectively. Of them, the 10 most frequently reported drugs are listed in Tables 2 and 3. As shown in Table 2, the most frequently reported AEs were cerebral hemorrhage (234 reports), interstitial lung disease (227 reports), and subcutaneous hemorrhage (157 reports). Focusing on RORs, 9 AEs in Table 2 yielded a positive signal, with a lower CI of the ROR greater than 1. Of note, there were noteworthy associations of clopidogrel with hepatocellular injury (ROR, 105.73; 95% CI, 82.8–135.0) and subcutaneous hemorrhage (ROR, 26.6; 95% CI, 22.5–31.4) after adjustment for age and sex.

Table 3 shows that the most frequently reported AEs for prasugrel were cerebral hemorrhage (ROR, 24.2; 95% CI, 18.0–32.4), followed by gastrointestinal hemorrhage (ROR, 23.6; 95% CI, 17.3–32.3) and anemia (ROR, 1.62; 95% CI, 1.02–2.56). There were noteworthy associations of prasugrel with melena (ROR, 165.7; 95% CI, 95.6–287.3), cardiac tamponade (ROR, 93.3; 95% CI, 49.2–176.8), and retroperitoneal hematoma (ROR, 61.9; 95% CI, 36.1–106.2). With

Table 2 The Top 10 Adverse Drug Events Associated with Clopidogrel

PT	n	Unadjusted			Adjusted		
		ROR	95% CI	*P* value	ROR	95% CI	*P* value
Cerebral haemorrhage	234	14.8	12.09–18.1*	<0.001	12.01	9.81–14.7*	<0.001
Interstitial lung disease	227	1.77	1.49–2.10*	<0.001	1.25	1.05–1.48*	0.012
Haemorrhage subcutaneous	157	31.2	26.4–36.8*	<0.001	26.6	22.5–31.4*	<0.001
Gastrointestinal haemorrhage	152	8.85	7.52–10.4*	<0.001	6.96	5.91–8.2*	<0.001
Agranulocytosis	147	6.44	5.46–7.59*	<0.001	7.49	6.34–8.84*	<0.001
Hepatic function abnormal	137	1.27	1.07–1.51*	0.006	1.34	1.13–1.59*	0.001
Anaemia	117	0.98	0.82–1.18	0.839	0.86	0.72–1.03	0.105
Haemorrhages	97	13.4	10.94–16.5*	<0.001	9.27	7.55–11.4*	<0.001
Hepatocellular injury	96	120.0	94.9–151.8*	<0.001	105.7	82.8–135.0*	<0.001
Gastric ulcer haemorrhage	87	1.51	1.22–1.87*	<0.001	1.35	1.09–1.66*	<0.001

Notes: *Signal detected. Adjusted for age (< 60s vs ≥ 60s) and sex (female vs male).
Abbreviations: CI, confidence interval; PT, preferred term; ROR, reporting odds ratio.

Table 3 The Top 10 Adverse Drug Events Associated with Prasugrel

PT	n	Unadjusted			Adjusted		
		ROR	95% CI	*P* value	ROR	95% CI	*P* value
Cerebral haemorrhage	50	31.3	23.4–42.0*	<0.001	24.2	18.0–32.4*	<0.001
Gastrointestinal haemorrhage	44	30.7	22.5–41.9*	<0.001	23.6	17.3–32.3*	<0.001
Anaemias	19	1.86	1.17–2.94*	0.008	1.62	1.02–2.56*	0.04
Subarachnoid haemorrhage	15	41.0	24.5–68.8*	<0.001	38.8	23.1–65.1*	<0.001
Shock haemorrhagic	15	40.6	24.3–68.1*	<0.001	34.7	20.7–58.3*	<0.001
Melaena	14	211.9	122.9–365.6*	<0.001	165.7	95.6–287.3*	<0.001
Retroperitoneal haematoma	14	90.4	52.8–154.6*	<0.001	61.9	36.1–106.2*	<0.001
Diverticulum intestinal haemorrhagic	11	12.9	7.08–23.4*	<0.001	10.2	5.60–18.5*	<0.001
Upper gastrointestinal haemorrhage	10	56.2	29.9–105.6*	<0.001	43.1	22.9–81.1*	<0.001
Cardiac tamponade	10	112.0	59.3–211.3*	<0.001	93.3	49.2–176.8*	<0.001

Notes: *Signal detected. Adjusted for age (< 60s vs ≥ 60s) and sex (female vs male).
Abbreviations: CI, confidence interval; PT, preferred term; ROR, reporting odds ratio.

prasugrel, AEs ranked relatively highly with clopidogrel, interstitial lung disease and liver injury (abnormal hepatic function and hepatocellular injury), were not ranked highly.

Discussion

In this study, the JADER database was used to clarify the characteristics of patients treated with clopidogrel and prasugrel. AEs of clopidogrel and prasugrel tended to show a peak age of onset in patients in their 70s and 70s-80s, respectively. Adverse drug reactions of clopidogrel and prasugrel occurred more often in men. Bleeding complications were commonly detected for both clopidogrel and prasugrel, whereas interstitial lung disease, abnormal hepatic function, and hepatocellular injury ranked higher with clopidogrel than with prasugrel. To the best of our knowledge, this is the first study to show differences in the adverse event profiles of clopidogrel and prasugrel in real-world practice based on the JADER pharmacovigilance database.

According to the 2019 ACC/AHA Guidelines on the Primary Prevention of Cardiovascular Disease, a double-therapy regimen (oral anticoagulant plus single antiplatelet therapy with a P2Y12 inhibitor) is recommended for patients with atrial fibrillation (AF) and coronary heart disease.[16] This anticoagulation therapy causes an increased risk of hemorrhagic events. In the present study, report frequency differed between the two groups (clopidogrel, 5869 AE reports; prasugrel, 513 AE reports); however, the patients' characteristics in these groups were similar. Furthermore, bleeding complications were often reported with both clopidogrel and prasugrel in the JADER database.

However, the results showed some differences in AEs between clopidogrel and prasugrel. First, clopidogrel was significantly associated with interstitial lung disease, whereas prasugrel was not. This is consistent with a case report showing subacute interstitial pneumonia caused by clopidogrel using a lung biopsy specimen.[17] In addition, clopidogrel-induced lung injury has been reported, including bleeding events such as alveolar hemorrhage, as well as interstitial lung diseases such as eosinophilic pneumonia or organizing pneumonia.[18,19] Furthermore, a retrospective, cohort study showed that the incidence of community-acquired pneumonia was significantly greater in patients receiving clopidogrel (OR, 3.39; 95% CI 3.27–3.51, $P < 0.0001$), which remained after adjustment (OR, 1.48; 95% CI 1.41–1.55, $P < 0.0001$).[20] Conversely, clinical studies suggest that antiplatelet agents may be associated with better outcomes in patients with pneumonia.[21,22] The mechanism underlying the conflicting effects of antiplatelet agents on pulmonary tissue is that platelets contribute to the host defense against bacterial infectious agents by limiting vascular lesions and inducing injury repair,[23] whereas unbalanced platelet activation may have pathological consequences. Indeed, platelet activation may exacerbate acute lung injury by promoting the recruitment of neutrophils and release of pro-inflammatory mediators.[24] Second, clopidogrel was significantly associated with liver injury. This is consistent with experimental studies.[25,26] Metabolites of clopidogrel produced by CYP3A4 have toxicity for hepatocytes via mitochondrial damage and cytochrome C release, eventually promoting apoptosis and/or necrosis.[26] However, clopidogrel shows decreased hepatic

necroinflammation by inhibition of platelet aggregation.[27] There are several reports that platelets have harmful effects on the liver. Platelets bind to the endothelium, causing the endothelium to upregulate and secrete chemokine (C-C motif) ligand 2 (CCL-2) and chemokine (C-X-C motif) ligand 8 (CXCL-8), which recruit T cells and neutrophils to the endothelium. Clopidogrel inhibits dense granule release. Platelets also drive fibrosis and produce transforming growth factor (TGF)-β, platelet-derived growth factor (PDGF)-β, and CXCL4 to aid conversion of hepatic stellate cells into collagen-producing myofibroblasts.[28,29] Indeed, clopidogrel has been shown to have an anti-fibrotic effect against carbon tetrachloride (CCl4)-induced liver fibrosis in rats by reduction of TGF-β1.[30]

As with any pharmacovigilance study, the present study has several limitations, including reporting bias, signal strength, and lack of detailed clinical data. The JADER database is subject to under-reporting and over-reporting biases. These reporting biases can affect the accuracy and completeness of the data, potentially influencing the observed AE profiles. The ROR provides an estimate of the association between a drug and an AE, but does not measure the absolute risk or the strength of the signal. It reflects the likelihood of a drug being reported in association with an AE compared to all other drugs, rather than the actual incidence of the AE. Finally, the JADER database lacks detailed clinical information, such as patients' medical histories, family histories, and the etiology of underlying diseases. This limits our ability to fully understand the context and causality of the reported AEs.

Conclusion

In conclusion, the present study showed three main findings. First, the study showed the rank-order of AEs associated with clopidogrel and prasugrel using a nationwide pharmacovigilance database (JADER). Second, common AEs were identified. Bleeding complications were found to be common AEs for both drugs in the present study. This finding is well-supported by the study's analysis and is consistent with known side effects of antithrombotic therapy. Finally, differences in AEs between clopidogrel and prasugrel, specifically interstitial lung disease, hepatic function abnormalities, and hepatocellular injury with clopidogrel, were found. This differentiation is a key finding of this study.

Abbreviations

AE, adverse event; CI, confidence interval; ROR, reporting odds ratio.

Acknowledgments

K. Hosohata received research support from the Science Research Promotion Fund.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Gurbel PA, Bliden KP, Hiatt BL, O'Connor CM. Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. *Circulation*. 2003;107:2908–2913. doi:10.1161/01.CIR.0000072771.11429.83
2. Simon T, Bhatt DL, Bergougnan L, et al. Genetic polymorphisms and the impact of a higher clopidogrel dose regimen on active metabolite exposure and antiplatelet response in healthy subjects. *Clin Pharmacol Ther*. 2011;90:287–295. doi:10.1038/clpt.2011.127
3. Sorich MJ, Rowland A, McKinnon RA, Wiese MD. Cyp2c19 genotype has a greater effect on adverse cardiovascular outcomes following percutaneous coronary intervention and in asian populations treated with clopidogrel: a meta-analysis. *Circulation*. 2014;7:895–902. doi:10.1161/CIRCGENETICS.114.000669
4. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *New Engl J Med*. 2007;357:2001–2015. doi:10.1056/NEJMoa0706482
5. Brandt JT, Close SL, Iturria SJ, et al. Common polymorphisms of cyp2c19 and cyp2c9 affect the pharmacokinetic and pharmacodynamic response to clopidogrel but not prasugrel. *J Thromb Haemost*. 2007;5:2429–2436. doi:10.1111/j.1538-7836.2007.02775.x
6. Organization WH. *The Safety of Medicines in Public Health Programmes: Pharmacovigilance an Essential Tool*. Geneva, Switzerland: WHO Press, World Health Organization; 2006.
7. Ramirez E, Carcas AJ, Borobia AM, et al. A pharmacovigilance program from laboratory signals for the detection and reporting of serious adverse drug reactions in hospitalized patients. *Clin Pharmacol Ther*. 2010;87:74–86. doi:10.1038/clpt.2009.185
8. Kambara H, Oyama S, Inada A, Niinomi I, Wakabayashi T, Hosohata K. Current status of adverse event profile of tacrolimus in patients with solid organ transplantation from a pharmacovigilance study. *Int J Clin Pharmacol Ther*. 2021;59:753–759. doi:10.5414/CP204016

9. Wakabayashi T, Ueno S, Nakatsuji T, et al. Safety profiles of new xanthine oxidase inhibitors: a post-marketing study. *Int J Clin Pharmacol Ther*. 2021;59:372–377. doi:10.5414/CP203898
10. Kambara H, Hosohata K, Nakatsuji T, et al. Safety profile of vonoprazan compared with proton pump inhibitors: insight from a pharmacovigilance study. *Pharmazie*. 2020;75:527–530. doi:10.1691/ph.2020.0604
11. Niinomi I, Hosohata K, Oyama S, Inada A, Hirai T, Iwanaga K. Drug-induced thrombotic microangiopathy using the Japanese pharmacovigilance database. *Int J Clin Pharmacol Ther*. 2020;58:543–549. doi:10.5414/CP203724
12. Niinomi I, Hosohata K, Oyama S, Inada A, Wakabayashi T, Iwanaga K. Pharmacovigilance assessment of drug-induced acute pancreatitis using a spontaneous reporting database. *Int J Toxicol*. 2019;38:487–492. doi:10.1177/1091581819870717
13. Inada A, Oyama S, Niinomi I, Wakabayashi T, Iwanaga K, Hosohata K. Association of Stevens-Johnson syndrome and toxic epidermal necrolysis with antiepileptic drugs in pediatric patients: subgroup analysis based on a Japanese spontaneous database. *J Clin Pharm Ther*. 2019;44:775–779. doi:10.1111/jcpt.13001
14. Hosohata K, Oyama S, Niinomi I, Wakabayashi T, Inada A, Iwanaga K. Comparison of safety profiles of new oral anticoagulants with warfarin using the Japanese spontaneous reporting database. *Clin Drug Investig*. 2019;39:665–670. doi:10.1007/s40261-019-00788-3
15. Hosohata K, Inada A, Oyama S, Niinomi I, Wakabayashi T, Iwanaga K. Adverse cutaneous drug reactions associated with old- and new- generation antiepileptic drugs using the Japanese pharmacovigilance database. *Clin Drug Investig*. 2019;39:363–368. doi:10.1007/s40261-019-00754-z
16. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 acc/aha guideline on the primary prevention of cardiovascular disease: executive summary: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. *Circulation*. 2019;140:e563–e595. doi:10.1161/CIR.0000000000000677
17. Tomoda Y, Miyajima T, Nagasawa C, Awaya Y. Clopidogrel-induced pneumonia. *BMJ Case Rep*. 2021;14:e244564. doi:10.1136/bcr-2021-244564
18. Gill DS, Ng K, Ng KS. Massive pulmonary haemorrhage complicating the treatment of acute coronary syndrome. *Heart*. 2004;90:e15. doi:10.1136/hrt.2003.028589
19. Inagaki Y, Tachibana K, Inoue Y, Kasai T, Inoue Y. Severe clopidogrel-induced dress with eosinophilic pneumonia associated with Epstein-Barr virus reactivation. *Respirol Case Rep*. 2020;8:e00541. doi:10.1002/rcr2.541
20. Gross AK, Dunn SP, Feola DJ, et al. Clopidogrel treatment and the incidence and severity of community acquired pneumonia in a cohort study and meta-analysis of antiplatelet therapy in pneumonia and critical illness. *J Thromb Thrombolysis*. 2013;35:147–154. doi:10.1007/s11239-012-0833-4
21. Winning J, Reichel J, Eisenhut Y, et al. Anti-platelet drugs and outcome in severe infection: clinical impact and underlying mechanisms. *Platelets*. 2009;20:50–57. doi:10.1080/09537100802503368
22. Winning J, Neumann J, Kohl M, et al. Antiplatelet drugs and outcome in mixed admissions to an intensive care unit. *Crit Care Med*. 2010;38:32–37. doi:10.1097/CCM.0b013e3181b4275c
23. Engelmann B, Massberg S. Thrombosis as an intravascular effector of innate immunity. *Nat Rev Immunol*. 2013;13:34–45. doi:10.1038/nri3345
24. Lynn MR. Instrument reliability and validity: how much needs to be published? *Heart Lung*. 1989;18:421–423.
25. Zhai Y, Wang L, Yang F, et al. The mechanism and risk factors of clopidogrel-induced liver injury. *Drug Chem Toxicol*. 2016;39:367–374. doi:10.3109/01480545.2015.1122606
26. Zahno A, Bouitbir J, Maseneni S, Lindinger PW, Brecht K, Krahenbuhl S. Hepatocellular toxicity of clopidogrel: mechanisms and risk factors. *Free Radic Biol Med*. 2013;65:208–216. doi:10.1016/j.freeradbiomed.2013.06.007
27. Iannacone M, Sitia G, Narvaiza I, Ruggeri ZM, Guidotti LG. Antiplatelet drug therapy moderates immune-mediated liver disease and inhibits viral clearance in mice infected with a replication-deficient adenovirus. *Clin Vaccine Immunol*. 2007;14:1532–1535. doi:10.1128/CVI.00298-07
28. Ripoche J. Blood platelets and inflammation: their relationship with liver and digestive diseases. *Clin Res Hepatol Gastroenterol*. 2011;35:353–357. doi:10.1016/j.clinre.2011.02.012
29. Dooley S, ten Dijke P. Tgf-beta in progression of liver disease. *Cell Tissue Res*. 2012;347:245–256. doi:10.1007/s00441-011-1246-y
30. Mahmoud NI, Messiha BAS, Salehc IG, Abo-Saif AA, Abdel-Bakky MS. Interruption of platelets and thrombin function as a new approach against liver fibrosis induced experimentally in rats. *Life Sci*. 2019;231:116522. doi:10.1016/j.lfs.2019.05.078