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The use of a low-flux hemo-dialyzer is associated with impaired platelet aggregation in patients undergoing chronic hemodialysis

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Abstract

In patients with chronic hemodialysis (HD), both abnormal thrombotic and bleeding events are commonly observed. Uremic platelet dysfunction is one of the important attributing factors. Moreover, HD may also result in aggregation dysfunction of platelets during the therapeutic procedure. However, how the HD process affects platelet and coagulation function is unknown and dialyzer membrane flux could have an impact on it. We aimed to compare the impacts of low-flux and high-flux HD on the platelet function of patients undergoing chronic HD. This was a cross-sectional study conducted in the HD unit of E-Da hospital in Taiwan. A total of 78 patients with maintenance HD three times per week for more than one year, including 40 with high- and 38 with low-flux hemodialysis, were recruited. Their platelet functions were evaluated using an in vitro platelet function analyzer (PFA-100) before and after the HD session. Of the 78 patients undergoing HD, 60 (76%) had prolonged pre-dialysis collagen/epinephrine (CEPI) and collagen/adenosine diphosphate closure times. Those receiving low-flux dialyzer had a significant increase in CEPI closure time (pre-dialysis 212.3 ± 62.1 seconds. post-dialysis 241.5 ± 64.3 seconds, $P = .01$), but not collagen/adenosine diphosphate closure time, after HD. After adjusting confounding factors, only the low-flux dialyzer demonstrated an independent association with the prolonged CEPI closure time after HD therapy (odds ratio = 23.31, 95% CI: 1.94–280.61, $P = .01$). We observed that impaired platelet aggregation is prevalent in patients undergoing chronic HD. Therefore, the use of low-flux dialyzers may further worsen platelet aggregation after dialysis. Patients with uremic bleeding diathesis should take precautions. We suggest that further studies using flow cytometry should be conducted to explore the mechanism of dialysis flux and platelet activity during HD.

Abbreviations: ADP = adenosine diphosphate, APTT = activated partial thromboplastin time, BUN = blood urea nitrogen, CADP = collagen/adenosine diphosphate, CEPI = collagen/epinephrine, Hct = hematocrit, HD = hemodialysis, hs-CRP = high-sensitivity C-reactive protein, PFA-100 = platelet function analyzer, PT = prothrombin time, vWF = von Willebrand factor.

Keywords: biocompatibility, dialyzer membrane, hemodialysis, platelet activation, platelet function analyzer

1. Introduction

Patients with end-stage renal disease have platelet dysfunction that includes impaired platelet-platelet or platelet-vessel wall interactions.[1] However, even patients who receive hemodialysis (HD) adequately, suffer from thrombotic and bleeding diathesis.[2] Furthermore, the dialysis procedure itself has been demonstrated to impinge this diathesis.[3,4] At the beginning of the HD session, platelets are activated and degranulated, after which there is an aggregation. Afterward, these repeated platelet activations may lead to exhaustion and attenuated aggregation along the course of HD. This biphasic phenomenon was confirmed by Aggarwal et al[5] Dialysis setting, membrane biocompatibility, geometric design of dialyzer, and the amount of uremic toxins removal have been reported to be involved in intradialytic platelet dysfunctions.[6–8] However, these study results are diverse, and the mechanisms behind these abnormalities are still inconclusive.[9,10] Accordingly, it is mandatory to reevaluate the impacts of dialysis settings on platelet function during HD sessions.

Platelet function analyzer-100 (PFA-100), is a device used to estimate the time required for flowing whole blood to occlude

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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two disposable cartridges: collagen/epinephrine (CEPI) and collagen/adenosine diphosphate (CADP), under higher shearing stress, are usually applied to evaluate the combined capabilities of platelet adherence and aggregation. In this device, epinephrine and adenosine diphosphate (ADP) were adopted as agonists for platelet aggregation in CEPI and CADP, respectively. Epinephrine can stimulate platelet degranulation and release substances such as ADP for platelet activation. ADP further binds to the ADP receptor on the platelet surface and induces the active conformation of glycoprotein 2b/3a receptor, through which it can bind to fibrinogen and other platelets.[11] PFA-100 was superior to other conventional analyzers for bleeding time calculation in vitro blood clotting at high shearing stress.[12] It had been demonstrated that the closure time measurement using PFA-100 was depicted to be more sensitive and specific than the skin bleeding time and platelet aggregation test did in patients with chronic HD.[13,14]

Furthermore, dialyzer membranes differ in geometric design, biocompatibility, polyvinylpyrrolidone content, sterilization method, and heparin dosing requirement, all of which affect platelet activation during HD sessions.[15,16] In clinical practice, low-flux dialyzers have relatively smaller pore size, lower ultrafiltration coefficient, less efficacy in removing middle-size uremic toxins, and a smaller amount of heparin consumed than high-flux dialyzers did.[17,18] However, it is not clear that these two types of dialyzers may own different impacts on platelet function in HD patients.

Therefore, by applying PFA-100, we aimed to clarify and compare the impact on platelet function in patients with chronic HD who underwent low-flux or high-flux dialysis.

2. Materials and methods

2.1. Study design

This was a single-center, cross-sectional study conducted in the HD unit of E-Da hospital.

2.2. Participants

Patients older than 20 years and had been undergoing HD therapy for more than 6 months, trice weekly and 4 hours per session, were recruited. The decision to use either low- or high-flux HD therapy was made by their nephrologists-in-charge according to their clinical judgment. Patients with a history of acute bleeding, acute thromboembolic events, or use of anti-platelet agents (Aspirin, Dipyridamole or Clopidogrel), anticoagulants, conjugated estrogens, and non-steroid anti-inflammatory drugs within 1 month before entry were excluded. All patients were given informed consent. The study complied with the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of I-Shou University (ISU95-04-25).

2.3. Sample collection

Fasting blood samples were obtained before and immediately after a mid-week HD session. The blood samples were centrifuged at 3000 revolutions per minute for 10 min for biochemical analyses within 1 hour after collection. All the measurements included blood urea nitrogen (BUN), complete blood counts, high-sensitivity C-reactive protein (hs-CRP), prothrombin time (PT), activated partial thromboplastin time (APTT), antithrombin III, fibrinogen, von Willebrand factor (vWF), protein C, and protein S. PT and APTT were measured by Cephalin-Kaolin reagent (EXBIO, Olomouc s.r.o., Ovesn, Czech Republic), and antithrombin III by Accuclot Heptest kit (Sigma Diagnostics, Inc., St. Louis, MO). vWF were measured by enzyme-linked immunosorbent assay (ELISA, Behringwerke AG, Marburg, Germany) and fibrinogen by a clotting assay (Multi. bren, Behring). Protein C and protein S were determined by amidolytic assays (Spectrolyse/fibrin, Biopool). Hemoglobin, hematocrit (Hct) and platelet count were determined by a Sysmex hematology analyzer. BUN and hs-CRP were determined by bromcresol green (chemicals manufactured by HUMAN, Wiesbaden, Germany).

2.4. Platelet function analyzer-100 (PFA-100)

The whole blood was immediately anticoagulated with 3.2% buffered citrate and using the PFA-100™ (Dade Behring, Marburg, Germany) to check platelet function. The blood sample was sent for investigation within 4 hours after collection. PFA-100 monitored platelet interaction on two cartridges. Both held a membrane with a 150 μm aperture and separately coated with collagen and either epinephrine or ADP for CEPI or CADP cartridge. This instrument provided a closure time which was determined by the time required for the platelet plug to occlude the aperture and was expressed in seconds. The normal range of the closure time is 85 to 165 seconds for CEPI and 71 to 118 seconds for CADP in the general population.

2.5. Statistical methods

To compare the paired data between pre- and post-dialysis in all patients, we performed paired Student's *t* test for parameters with normal distribution and Wilcoxon signed rank test for those without normal distribution. Pearson's correlation tests were adopted to identify the relationships between "ultrafiltration rate" and variable parameters. To compare the data between the two subgroups, Chi-square test was used for categorical variables. Independent sample Student's *t* test was used for parameters with normal distribution, Mann–Whitney *U* test was used for those without normal distribution. Binary logistic regression was used to estimate the odds ratios to achieving a prolonged CEPI closure time after HD therapy for multiple possible variables. Data were presented with a mean ± standard deviation (SD). Distribution of parameters were examined using Levene's test of homogeneity of variance. A P value < .05 was considered statistically significant. SPSS 19 for Windows (SPSS Inc., Chicago, IL) was used for statistical analysis.

3. Results

A total of 150 chronic HD patients were screened, and 78 were enrolled. Of these participants, 46 were men and 32 were women with a mean age of 62.1 ± 12.3 years. All the patients received unfractionated heparin during HD treatment with a mean dosage of 2256.1 ± 959.3 units per session. Among them, 51 patients (65.4%) had native arteriovenous fistula as their vascular access, and 27 patients (34.6%) had artificial grafts. Thirty-eight patients (48.7%) received low-flux dialysis using polyamide dialyzer (Gambro polyflux 14 L, 17 L, 21 L) for HD therapy and the rest of the 40 patients (51.3%) received high-flux dialysis using either polysulfone (Fresenius FX-class 60, 80, 100) or polyamide dialyzer (Gambro polyflux 17 S, 21 S).

3.1. Comparison of pre-dialytic and post-dialytic PFA-100 and other parameters

Regarding the pre-dialytic CEPI and CADP closure time, we observed that 60 (76.9%) and 55 (70.5%) of our 78 HD patients had prolonged CEPI and CADP closure time than the normal references, respectively. There was no significant difference between pre- and post-dialytic CEPI or CADP closure time, despite a significant increase in post-dialytic platelet counts, hs-CRP, pro-coagulants (hematocrit, fibrinogen, and vWF), anti-coagulants (protein C and anti-thrombin III), and decrease of BUN and PT levels. APTT and protein S

remained unchanged before and after the HD session (Table 1). Comparison of pre- and post-dialytic changes between the two dialyzer groups was consistent with that of the whole population, except post-dialytic CEPI, which increased in the low flux dialyzer group (Table S1, Supplemental Digital Content, http://links.lww.com/MD/H856). The mean ultrafiltration rate of the studied HD session was 3.1 ± 1.8%. These ultrafiltration rates were significantly correlated with the percentage changes of Hct (R^2 = 0.474, P = .000), platelet (R^2 = 0.318, P = .000), fibrinogen (R^2 = 0.217, P = .002), protein C (R^2 = 0.116, P = .031), vWF (R^2 = 0.276, P = .001), antithrombin III (R^2 = 0.175, P = .007), and hs-CRP (R^2 = 0.104, P = .042) during HD session (Table S2, Supplemental Digital Content, http://links.lww.com/MD/H857).

3.2. Comparison of high-flux and low-flux dialysis

While comparing with high-flux (N = 40, 51.3%) dialysis group to low-flux (N = 38, 48.7%), we observed less pre-dialysis CEPI closure time in low-flux dialysis patients (low-flux vs high-flux: 212.3 ± 62.1 s vs 241.8 ± 60.4 s, P = .038). There was significant prolongation of post-dialytic CEPI closure time, but not CADP closure time (pre-dialytic CEPI 212.3 ± 62.1 s vs post-dialytic CEPI 241.5 ± 64.3 s, P = .010) in low-flux dialysis patients. For patients on high-flux dialyzer, the differences between pre-dialytic and post-dialytic CEPI or CADP closure time were not observed. In comparison to high-flux, patients undergoing low-flux hemodialysis had lower dry weight (64.9 ± 13.8 kg vs 54.2 ± 10.5 kg, P = .004), lower arterial blood flow (286.7 ± 131.6 mL/min vs 257.9 ± 138.6 mL/min, P = .011), and lower heparin dosage (2923 ± 1132.5 units vs 1946.4 ± 692.6 units, P = .002). There were no differences in sex, age, Hct, platelet count, PT, APTT, fibrinogen, protein C, protein S, vWF, anti-thrombin III, BUN, and hs-CRP levels between 2 groups (Table 2).

3.3. Factors associated with prolongation of CEPI closure time

Regarding the magnitude of change (Δ, post-dialysis minus pre-dialysis) in CEPI and CADP closure time, our data delineated that the ΔCEPI was significantly higher in patients on low-flux dialysis than that in patients on high-flux dialysis. Whereas, ΔCADP remained unchanged between the two groups (Table 2). When we stratified our patients by prolonging CEPI closure time (ΔCEPI > 0 s vs ≦0 s), we discovered only the type of dialyzer, but not ultrafiltration volume or heparin dosage, remained as the significant parameter that correlated with this prolongation. There were 26 (66.7%) patients receiving low-flux dialyzer who had prolonged CEPI (P = .002, Table 3). Using a binary logistic regression model to examine the significant parameters that contributed to the prolongation of CEPI closure time, we observed that patients receiving low-flux (vs high-flux) dialyzer had an odds ratio of 23.31 (95% CI: 1.94–280.61, P = .013) after adjusting for age, dialysis blood flow, ultrafiltration rate, heparin dosage, Hematocrit, and platelet count (Table 4).

4. Discussion

In the current study, 60 (76.9%) and 55 (70.5%) of our 78 patients with HD had prolonged pre-dialytic CEPI and CADP closure time than normal participants. Our study also revealed patients with uremia may have increased bleeding risk even with normal coagulation test results and absolute platelet counts. We found the presence of impaired baseline platelet aggregation in more than 70% of maintenance HD patients. However, there was no improvement in post-dialytic CEPI or CADP closure time, which was contrary to other reports with beneficial results in HD patients.[10,19] Similar to other studies, there were significant increase in Hct, platelet count, pro-coagulants (fibrinogen and vWF), and anti-coagulants (protein C and anti-thrombin III) after the course of hemodialysis.[19] The increase in serum platelet count, Hct, pro-coagulants, and anti-coagulants may be due to the hemoconcentration effect by the ultrafiltration process during the HD session, which may interfere with the interpretation of coagulation or platelet function tests. PFA-100 clotting time was reported to be prolonged by significant reduction in platelet count or Hct.[20] In previous studies of PFA-100, the improvement of the prolonged closure times toward normal was hypothesized to have resulted from uremic toxins removal by HD. However, significant hemoconcentration by ultrafiltration may also reduce platelet aggregation time as well, which may cause post-dialytic normalization of PFA-100 as observed in previous studies. However, in our study, there was no significant change in either CEPI or CADP closure time after HD. The ultrafiltration volume (3.1 ± 1.8%) in our HD patients were relatively small. The post-dialytic Hct increasement in our study was lower compared with that reported by Mekawy et al[10] This may explain the reason why the PFA-100 clotting times remained unchanged after HD.

Another main finding was a significant prolongation of CEPI closure time after HD session in patients using low-flux, but

Table 1

Comparison of pre- and post-dialytic parameters in 78 patients.

Parameters	Pre-dialytic	Post-dialytic	*P*
CEPI (s)	227.8 ± 62.7	234.5 ± 66.6	ns
CADP* (s)	164.6 ± 70.8	164.0 ± 77.6	ns
Hematocrit (%)	31.5 ± 3.5	33.1 ± 3.6	<.001
Platelet count (×1000/μL)	196.0 ± 56.2	212.3 ± 53.2	<.001
PT* (s)	11.3 ± 1.5	10.7 ± 1.2	<.001
APTT* (s)	39.2 ± 36.1	36.5 ± 14.9	ns
Fibrinogen (mg/dL)	352.1 ± 52.4	381.5 ± 60.5	<.001
Protein C (%)	120.2 ± 17.4	128.9 ± 22.5	<.001
Protein S (%)	86.4 ± 14.9	83.3 ± 16.2	ns
von Willebrand factor* (%)	171.2 ± 82.2	190.4 ± 97.7	<.001
Antithrombin-III* (%)	90.8 ± 14.3	98.8 ± 18.5	<.001
BUN (mg/dL)	71.1 ± 16.0	20.3 ± 7.0	<.001
hs-CRP (mg/dL)	0.6 ± 0.2	0.7 ± 0.2	.004

APTT = activated partial thromboplastin time, BUN = blood urea nitrogen, CADP = collagen/adenosine diphosphate, CEPI = collagen/epinephrine, hs-CRP = high sensitivity C-reactive protein, ns = non significance, PT = prothrombin time, s = second.

*Wilcoxon signed rank test was conducted for these variables.

Table 2

Comparison of parameters between patients receiving high-flux and low-flux dialyzer.

Parameters	High-flux N = 40 (51.3%)	Low-flux N = 38 (48.7%)	*P*
CEPI*			
Pre-dialysis (s)	241.8 ± 60.4	212.3 ± 62.1	.042
Post-dialysis (s)	228.1 ± 68.7	241.5 ± 64.3	ns
CADP*			
Pre-dialysis (s)	161.0 ± 70.2	167.0 ± 72.1	ns
Post-dialysis (s)	152.3 ± 76.8	176.6 ± 77.4	ns
Δ CEPI (s)	-13.7 ± 64.4	29.4 ± 64.4	.005
Δ CADP (s)	-10.9 ± 77.8	10.6 ± 94.6	ns
Gender, male (%)	22 (55.0)	24 (63.2)	ns
Age (yr/o)	62.1 ± 12.2	62.1 ± 12.6	ns
Dry weight (kg)	64.9 ± 13.8	54.2 ± 10.5	.004
Blood flow* (mL/min)	286.7 ± 31.6	257.9 ± 38.6	.019
Heparin* (unit)	2923.1 ± 1132.5	1946.4 ± 692.6	.014
Ultrafiltration rate (%)	3.6 ± 2.1	2.9 ± 1.7	ns
Hematocrit (%)	31.5 ± 3.5	31.5 ± 3.5	ns
Platelet count* (×1000/μL)	186.7 ± 56.0	205.9 ± 55.5	ns
PT (s)	11.0 ± 1.4	11.6 ± 1.5	ns
APTT* (s)	33.6 ± 7.3	39.0 ± 28.1	ns
Fibrinogen (mg/dL)	353.8 ± 51.3	351.1 ± 54.0	ns
Protein C (%)	118.3 ± 15.2	121.4 ± 18.8	ns
Protein S (%)	86.0 ± 15.1	86.7 ± 15.0	ns
von Willebrand factor* (%)	171.5 ± 84.7	170.2 ± 80.7	ns
Antithrombin-III (%)	91.6 ± 11.4	89.9 ± 16.0	ns
BUN (mg/dL)	70.8 ± 16.7	71.4 ± 15.5	ns
hs-CRP (mg/dL)	0.4 ± 0.6	0.8 ± 0.3	ns

CADP = collagen/adenosine diphosphate, CEPI = collagen/epinephrine, ns = non significance, s = second, Δ CADP = post-dialysis CADP closure time – pre-dialysis CADP closure time, Δ CEPI = post-dialysis CEPI closure time – pre-dialysis CEPI closure time.

*Mann–Whitney *U* test was conducted for these variables.

Table 3

Comparison of parameters between patients with and without prolonged CEPI closure time during hemodialysis.

Parameters	Prolonged CEPI N = 39 (50.0%)	No prolonged CEPI N = 39 (50.0%)	*P*
Gender, male (%)	23 (59.0)	23 (59.0)	ns
Age (yr/o)	61.0 ± 11.7	63.1 ± 12.4	ns
Dry weight (kg)	58.1 ± 12.7	58.3 ± 14.1	ns
Blood flow* (mL/min)	268.8 ± 43.6	270.0 ± 33.5	ns
Heparin* (unit)	2260.4 ± 1008.7	2250.0 ± 978.6	ns
Ultrafiltration (%)	2.8 ± 1.7	3.5 ± 2.0	ns
Low-flux dialyzer (%)	26 (66.7)	12 (30.8)	.002
Hematocrit (%)	31.6 ± 3.4	31.4 ± 3.6	ns
Platelet count* (×1000/μL)	198.7 ± 57.8	193.4 ± 60.9	ns
PT* (s)	11.5 ± 1.4	11.1 ± 1.5	ns
APTT* (s)	36.6 ± 11.8	34.9 ± 26.2	ns
Fibrinogen (mg/dL)	355.0 ± 53.6	350.5 ± 52.9	ns
Protein C (%)	120.3 ± 17.5	120.7 ± 18.1	ns
Protein S (%)	87.9 ± 13.6	85.7 ± 15.4	ns
von Willebrand factor (%)	165.0 ± 73.3	180.1 ± 95.2	ns
Antithrombin-III* (%)	89.5 ± 15.6	92.1 ± 13.5	ns
BUN (mg/dL)	70.3 ± 17.8	71.9 ± 14.2	ns
hs-CRP (mg/dL)	0.6 ± 0.3	0.8 ± 0.4	ns

BUN = blood urea nitrogen, CEPI = collagen/epinephrine, hs-CRP = high sensitivity C-reactive protein, ns = non significance, s = second.

*Mann–Whitney *U* test was conducted for these variables.

not high-flux dialyzers. For CADP closure time, the post-dialytic difference was absent in either group. We hypothesized that the prolongation of CEPI closure time in the low-flux group resulted from platelet exhaustion after repeated activation during HD. As an agonist of CEPI closure time, epinephrine was unable to induce further platelet degranulation and finally led to the prolongation of CEPI. Meanwhile, ADP consistently induced glycoprotein 2b/3a maturation and platelet aggregation through the direct binding of the ADP receptor.[11] As demonstrated in Table 2, CADP did not prolong after dialysis in both groups. The transient worsening of platelet aggregation after HD had also been demonstrated by Sreedhara et al[21] In another study of the evaluation platelet function by PFA-100 in patients receiving double filtration plasmapheresis, as similar to our results, the authors also observed that CEPI, but not CADP, was prolonged after therapy.[22] These findings suggested that CEPI is

Table 4

Unadjusted and adjusted odds ratios for the presence of prolonged CEPI closure time during hemodialysis therapy in 78 patients.

	Unadjusted odds ratio (95% confidence interval)	Adjusted odds ratio* (95% confidence interval)
Low-flux vs high-flux	4.50 (1.73, 11.65)	23.31 (1.94, 280.61)
P value	.002	.013

CEPI = collagen/epinephrine.

*Adjusted factors: age, dialysis blood flow, ultrafiltration rate, heparin dosage, hematocrit, and platelet count.

more sensitive than CADP for detecting platelet exhaustion after HD, which may result from repeated platelet activation during hemodialysis.

Low-flux dialyzer is less efficient to remove middle-sized uremic toxins than a high-flux dialyzer does. It was reported to have more intercellular adhesion molecular-1 (ICAM-1) increment before and after dialysis than high-flux dialyzer.[23] Low-flux dialyzer was also associated with higher insulin-resistance and suppressed cellular immune response manifested by impaired interferon gamma production, even with the same CRP as high-flux.[24,25] Platelet activation is reported to be a component of dialysis biocompatibility.[15] Aggarwal et al[4] found continued dialysis decreased platelet activity using flow cytometry to investigate platelet function. The bio-incompatibility character of a low-flux dialyzer may exhaust the platelet more during dialysis and resulted in post-dialytic CEPI prolongation. In the present study, both low and high flux dialyzers were composed of synthetic membranes, contained polyvinylpyrrolidone, and all were sterilized by steam. Although the low-flux group applied less heparin dosage than the high-flux one, in our study, after adjusting confounders, the low-flux dialyzer was the only independent factor associated with post-dialytic CEPI prolongation.

Our results support that the application of a low-flux dialyzer may worsen platelet aggregation in HD patients. However, there are still several limitations that need to be addressed. First, this was not a randomized controlled trial and some baseline characteristics of low- or high-flux dialysis groups were different. However, after adjusting these confounding factors, the low-flux dialyzer was associated with the prolongation of CEPI closure time. Second, the study did not have a cross-over design, which may further confirm our findings. Third, other examinations to detect platelet activation, such as flow cytometry for platelet surface marker expression, were not conducted.

5. Conclusion

In conclusion, the present study identified that more than 70% of maintenance HD patients had impaired platelet function when using the PFA-100 measurement. We also observed that patients receiving low-flux hemodialysis had a significantly prolonged CEPI closure time, after adjusting for all confounding factors. This suggests that HD using a low-flux dialyzer may has an impact on platelet aggregation during the course of HD. Caution should be taken in patients with bleeding diathesis while using a low-flux dialyzer. Further studies using flow cytometry are needed to confirm our findings and explore the mechanisms of intradialytic platelet activation and dialyzer flux.

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Author contributions

S-YH and M-YC designed and performed the experiments and analyzed the data; H-HW, Y-CL, L-CH, and T-ML collected the cases. C-YC wrote the draft manuscript and table. S-YH directed the study and supervised the writing of the manuscript. S-YH and H-HL reviewed and edited the manuscript. All authors have read and approved the final version of the manuscript.

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