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Anti-inflammatory effect of high flux dialyzer surface area 2.6m^2 in high flux hemodialysis and hemodiafiltration

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Abstract

Dialysis therapy has remarkably evolved through the innovation in dialyzers and hemodialysis modalities, enhancing patients' quality of life. The efficacy of dialysis can be determined by measuring the reduction ratio (RR) of middle molecules such as Interleukin-6 (IL-6) and Procalcitonin. In our study, we tested a high-flux dialyzer, BIOPURE (Biorema) 260 HF, with a surface area (SA) of 2.6 m^2, in terms of IL-6 and Procalcitonin removal while performing high-flux hemodialysis (HF-HD) and post-dilution online hemodiafiltration (OL-HDF). This crossover study comprised 25 patients who received a session of HF-HD using the BIOPURE (Biorema) 260 H, followed by a session of post-dilution OL-HDF. A washout period of 2 weeks was instilled between the two sessions, during which the patients received HF-HD using high-flux dialyzers (maximum SA 2.0 m^2). All patients' pre/post dialysis concentrations of IL-6 and procalcitonin were measured. The dialyzer used in this study resulted in a significant IL-6 RR of 44.92±5.11% (p<0.001) with HDF and 32.48±5.72% (p<0.001) with HF-HD; and a procalcitonin RR of 50.32±3.94% (p<0.001) with HDF and 41.80±4.32% (p<0.001) with HF-HD. In conclusion, the dialyzer BIOPURE (Biorema) 260 HF (SA 2.6 m^2) is efficient in eliminating IL-6 and procalcitonin, especially with OL-HDF compared to HF-HD, with acceptable albumin loss in the dialysate.

Keywords: Albumin, High-flux, Hemodialysis, Hemodiafiltration.

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Introduction

The mortality of dialysis patients can in part be explained by an ageing population and increased prevalence of comorbid factors such as diabetes and hypertension. Moreover, there are a number of risk factors unique to uremia itself including accumulation of uremic toxins- in particular middle and large sized molecules, chronic inflammatory state, and mineral metabolism disorders.[1]

Uremic solutes are divided into three major classes: small water-soluble compounds (<500Da), middle molecular substances (0.5-40kDa) and protein bound solutes.[2] Middle molecular weight substances consist of small peptides which have been implied in inflammation and oxidative stress.[3]

Hemodiafiltration combines diffusive and convective solute removal in a single session providing better clearance of middle molecular weight solutes than conventional high-flux hemodialysis (HF-HD).[4]

Interleukin-6 (IL-6) is a member of family with a mass of 21-28kDa.It is a multifunctional cytokine produced by T cells, B cells, monocytes, fibroblasts, keratinocytes, endothelial cells, mesangial cells, and several tumor cells.[5] IL-6 is produced in response to infections and tissue injury, contributes to host defenses through the stimulation of acute phase responses, hematopoiesis and immune reactions.[6]

Plasma IL-6 level is higher in chronic renal failure patients than in the general population which is associated with higher mortality rates. It was found that some pro-inflammatory cytokines can be removed from extracorporeal circulation by convection.[7]

Procalcitonin (PCT) a polypeptide of 116amino acids (MW 116 kDa), is the precursor of calcitonin.PCT is produced in the C cells of the thyroid gland without hormone activity. It is produced and released in the peripheral circulation in response to endotoxin and inflammatory cytokines.[8]

PCT is more specific in diagnosing sepsis and bacterial infection than other inflammatory markers such as C reactive protein (CRP). However, it has been found at high levels in patients with reduced renal function and that these levels are reduced after dialysis.[9]

Regarding dialyzers, a class of dialyzers composed of a medium cut-off (MCO) membrane has recently garnered interest. The MCO membrane's customized pore sizes potentiate the removal of middle-high uremic toxins by providing a higher retention onset and molecular weight cut-off (MWCO).[10] Furthermore, unlike high cut-off membranes, the MWCO of the MCO membrane is slightly lower than that of albumin, preventing albumin loss during dialysis.[11,12] In addition, it allows for exceptional internal filtration without the need for replacement fluid, enabling additional convection during hemodialysis.[12]

At the Ain Shams University Specialized Hospital's dialysis center, we have previously conducted studies to evaluate the hemodiafiltration against high-flux hemodialysis. We also determined that the high-flux dialyzer 2.6 m is promising for free light chains removal in high-flux hemodialysis and in hemodiafiltration. In the present study we assessed IL-6 and Procalcitonin using a dialyzer SA of 2.6m² in HF-HD versus HDF.

Patients and Methods

This crossover study was conducted at the Ain Shams University Specialized Hospital's dialysis center. Our study population comprised 25 patients diagnosed with End-Stage Renal Disease for over six months. Our patients received four hourly hemodialysis sessions, thrice per week, with a blood flow ≥300 ml/min. Sodium bicarbonate dialysate was used, and unfractionated heparin was administered as anticoagulation. Patients with temporary dialysis catheters, active inflammation or infections, decompensated heart failure, and Child B or C liver cirrhosis were excluded.

Dialyzer and Dialysis conditions

Each patient received two hemodialysis sessions; one was HF-HD, while the other was post-dilution online hemodiafiltration (OL-HDF), using a high-flux dialyzer [BIOPURE (Biorema) 260 HF (SA 2.6 m^2, high-flux hollow fiber with steam sterilization, myoglobin SC 0.7, membrane cut-off value 40,000 Da; Allmed Medical Gmbh, Germany]. We instilled a washout period of two weeks between the two sessions, during which the patients received HF-HD using a dialyzer with a maximum SA of 2.0 m^2.

The conditions of the hemodialysis sessions remained unchanged regarding dialysate flow (Qd:500ml/min) and blood flow ≥300 ml/min, yet the ultrafiltration rate varied according to each patient's weight before each session. Regarding the post-dilution OL-HDF session, the substitution volume was ≥20 L for all patients.

The following laboratory tests were analyzed at baseline: Complete Blood Count, Blood Urea Nitrogen (BUN), Serum Creatinine, Sodium, Potassium, Calcium, and Phosphorus, Parathyroid hormone level (PTH), Ferritin, Iron, Total Iron Binding Capacity (TIBC), and Serum

Albumin. Data of these laboratory investigations were obtained from hospital records. In addition, serum IL-6 and procalcitonin were measured, and appropriate calculations were made as follows:

Serum Interleukin-6

Serum IL-6 levels were measured before and after the two modalities of hemodialysis (HF-HD and post-dilution OL-HDF) for each patient. All blood samples were collected from the arterial line at the beginning and end of the dialysis session. The collected samples were allowed to rest for 10 – 20 minutes, at room temperature, to clot, then centrifuged at 704 xg for 20 minutes, after which the supernatant was removed. If precipitation appeared, centrifugation was repeated. IL-6 levels were measured using commercial kits based on a double antibody sandwich enzyme-linked immunosorbent (ELISA) assay (Catalogue No. 201-12-1093Shanghai Sunred Biological Technology Co., Ltd., China), according to the manufacturer's instructions.

The optical density (OD) of the final ELISA product was measured at 450 nm wavelength using a microtiter reader (The Awareness Technology Stat Fax 2100 microplate reader, Awareness Technology inc, USA). According to the standard's concentration and the corresponding OD value, a standard curve linear regression equation was calculated then the OD values of the samples were applied to the regression equation to calculate the corresponding sample's concentration.

The minimum detectable dose of Human IL-6 was determined to be 0.586 mg/L (Assay range: 0.6 mg/L-180 mg/L). The sensitivity of this assay was established by sub-tracing two standard deviations to the mean OD values of twenty zero standard replicates and calculating the corresponding concentration.

Procalcitonin

Procalcitonin levels were measured before and after each patient's two modalities of hemodialysis (HF-HD and post-dilution OL-HDF). All blood samples were collected from the arterial line at the beginning and end of the dialysis session. The collected samples were allowed to rest for 10 – 20 minutes, at room temperature, to clot, then centrifuged at 704 xg for 20 minutes, after which the supernatant was removed. If precipitation appeared, centrifugation was repeated.

Procalcitonin was estimated using a human EISA kit. Standards and samples were added to the corresponding wells, and procalcitonin present in a sample was bound to the wells by the antibody. The wells were washed, then procalcitonin antibodies labelled with biotin were added, combined with Streptavidin-Horseradish Peroxidase (HRP), to form an immune complex. This was followed by incubation and another wash to remove the uncombined enzyme. Chromogen solutions A and B were added next, resulting in the color of the liquid transforming to blue. On adding the Stop Solution, the color immediately became yellow. (The sensitivity of this assay was defined as the lowest protein concentration that could be differentiated from zero. It was determined by sub-tracing two standard deviations to the mean optical density value of twenty zero standard replicates and calculating the corresponding concentration). Assay range: 6pg/ml-2000pg/ml.

Calculations

IL-6 RR was calculated using the equation[15]

$$RR = \frac{Cpre\text{-}Cpost}{Cpre} \times 100\ \%$$

RR: reduction ratio, $C_{pre,}$ and c_{post} are serum IL-6 concentrations, pre-, and post-treatment, respectively.

Calculating IL-6 post-dialysis concentration corrected for net ultrafiltration, with the following equation [15]

$$Cpost.c = \frac{Cpost}{\left(1 + \frac{\Delta BW}{0.2 \times BWpost}\right)}$$

C post. c: serum IL-6 level post session after correction of net UF, C_{post} is serum IL-6 level post-session, BW_{post} is the body weight after ultrafiltration.

Cumulative albumin loss was measured by the following equations[15,16]

Cumulative dialysate Albumin (gm)

= *Albumin* ½ hr + *Albumin* 1st hr + *Albumin* 2nd hr

+ *Albumin* 3rd hr+ *Albumin* 4th hr

Albumin lost over the first half or 1st hour was measured by equation "A"[15,16]

$$Albumin\ (gm) = \frac{Dialysate\ Alb\ (mg/dl)}{100} \times \frac{[Quf + Sub\ volume + Qd\ (ml/min)]\ X30\ (mins)}{1000}$$

Albumin lost over 2nd or 3rd, or 4th hours was measured by equation "B" [15,16]

$$Albumin\ (gm) = \frac{Dialysate\ Alb\ (mg/dl)}{100} \times \frac{[Quf + Sub\ volume + Qd\ (ml/min)]\ X60\ (mins)}{1000}$$

Qd: dialysate flow*, QUF: ultrafiltration rate, Sub. Volume: substitution volume (in case of HDF only).*

Statistical Analysis

Collected data were revised, coded, tabulated, and analyzed using Statistical Package for the Social Sciences (SPSS) software version 20.0. (IBM Corp., Armonk, N, USA). The Shapiro-Wilk test was used to verify the normality of distribution. Qualitative data are presented as numbers and percentages; quantitative data as mean ±standard deviation (±SD) for normally distributed data or median with interquartile ranges (IQR) for nonparametric data. In qualitative data, independent variables were analyzed using the Chi-Square (X^2) test. For quantitative data, a two-tailed independent t-test was used to compare two independent groups with normally distributed data, while the Mann–Whitney test was used for nonparametric data. Correlations were done using the Pearson correlation coefficient test (r). Significance was defined by the *p*-value where $p < 0.05$ is significant.

Results

Baseline characteristics of the study cohort regarding age and gender, as well as baseline laboratory data, are summarized in Table 1.

Table 1. Demographic and laboratory data for the 25 in all patients included in the study.

Variables	Mean ± SD
Age (years)	48.4 ± 11.4
Gender (M/F)	23/2
Dry weight (Kg)	85(75-95)
BMI	31.06 ± 5.47
Parathyroid hormone (pg/ml)	458.0 (175.0 – 679.0)
Calcium (mg/dl)	8.47 ± 0.69
Phosphorus(mg/dl)	5.34 ± 1.06
Sodium (mEq/L)	134.0 ± 4.47
Potassium (mEq/L)	5.39 ± 0.70
Ferritin (ng/ml)	848.7 (362.2 – 951.0)
Total iron binding capacity(µg/dl)	216.4 ± 42.69
Iron (µg/dl)	60.52 ± 18.91
Total Leucocytic Count (*10^3/ mm^3)	7.02 ± 1.65
Lymphocytes (%)	23.49 ± 7.57
Neutrophils (%)	65.14 ± 8.62
Hemoglobin (gm/dl)	10.65 ± 1.26
Hematocrit (%)	34.30 ± 3.41
Platelets (*10^3/mm^3)	208.7 ± 66.28

TIBC; total iron binding capacity, (M/F); male/female, SD; Standard deviation.

HDF parameters of the total studied patients included a mean ultrafiltration volume of 2.96±0.96 L, a mean substitution volume of 21.12±0.87 L, a mean convection volume of 24.06±0.86 L, and a mean blood flow of 341.6±19.08 ml/min. Furthermore, the average total processed blood was calculated as 81.98±4.58 L, and the average calculated filtration fraction as 29.42±1.59 %. (Table 2)

Table 2. Descriptive analysis of the 25 studied cases according to different hemodiafiltration parameters.

	Mean ± SD.
HCT (%)	34.30 ± 3.41
UF (Δ BW)	2.96 ± 0.96
BMI	31.06 ± 5.47
Substitution volume	21.12 ± 0.87
Convection volume	24.06 ± 0.86
Blood flow	341.6 ± 19.08
Total processed BL (L)	81.98 ± 4.58
Filtration Fraction	29.42 ± 1.59

SD: Standard deviation HCT: hematocrit, UF:ultrafiltration, BW:body weight, BL:blood.

Urea reduction rate was calculated and compared between the two modalities showing that patients on HDF have higher urea reduction ratio in comparison with patients on high flux dialysis with *p* value <0.001. (Table 3)

Table 3. Comparison between high-flux hemodialysis (HF-HD) and hemodiafiltration (HDF) according to Urea reduction rate (%).

URR (%)	HF-HD (n = 25)	HDF (n = 25)	*p* value
Mean ± SD.	65.17 ± 6.11	68.52 ± 6.62	<0.001

SD: Standard deviation. *p* value for comparing between HF-HD and HDF. *$P \leq 0.05$ is significant.

The IL-6 levels measured at pre-dialysis in HF-HD and HDF were statistically significant different (*p*=< 0.001). The BIOPURE (Biorema) 260 HF dialyzer resulted in a statistically significant reduction in the mean IL-6 level post-dialysis, as compared to pre-dialysis levels, in both HF-HD and HDF (*p*<0.001). Notably, HDF brought about a significantly higher IL-6 RR (44.92 ± 5.11%) in contrast to HF-HD (32.48 ± 5.72%) (*p*<0.001). (Table 4)

Table 4. Comparison between high-flux hemodialysis (HF-HD) and hemodiafiltration (HDF) regarding Interleukin-6 (IL-6) levels and reduction ratio.

IL-6	HF-HD	HDF	*p* value
C pre (ng/ml)	42.16 ± 13.59	48.40 ± 13.61	<0.001
C post (ng/ml)	28.36 ± 9.43	26.43 ± 7.0	<0.001
RR (%)	32.48 ± 5.72	44.92 ± 5.11	<0.001

C pre; pre-dialysis IL-6 concentration, C post; post-dialysis IL-6 concentration, HDF; Hemodiafiltration, HF-HD; High-flux Hemodialysis, RR; reduction ratio. *$p \leq 0.05$ is significant.

The measured procalcitonin levels revealed statistically significant difference between pre-dialysis in HF-HD and HDF (p=< 0.001). The BIOPURE (Biorema) 260 HF dialyzer resulted in a statistically significant reduction in the mean procalcitonin level post-dialysis, as compared to pre-dialysis levels, in both HF-HD and HDF (p<0.001). Notably, HDF brought about a significantly higher procalcitonin RR (50.32 ± 3.94%) in contrast to HF-HD (41.80 ± 4.32%) (p<0.001). (Table 5)

Table 5. Comparison between high-flux hemodialysis (HF-HD) and hemodiafiltration (HDF) regarding procalcitonin levels and RR.

Procalcitonin	HF-HD	HDF	*p* value
C pre (ng/ml)	146.40 ± 44.83	206.8 ± 37.91	<0.001
C post (ng/ml)	84.82 ± 25.15	102.2 ± 22.27	<0.001
RR (%)	41.80 ± 4.32	50.32 ± 3.94	<0.001

C pre; pre-dialysis Procalcitonin concentration, C post; post-dialysis procalcitonin concentration, HDF; Hemodiafiltration, HF-HD; High-flux Hemodialysis, RR; reduction ratio. *$p \leq 0.05$ is significant.

Discussion

Renal replacement therapy has witnessed remarkable progression, since its conception, through the advancement in dialyzers and hemodialysis modalities, reducing the complications of renal replacement therapy and improving patients' quality of life. The efficacy of dialysis can be assessed by measuring the RR of middle molecules, such as IL-6 and procalcitonin. In our study, we tested a high-flux dialyzer, BIOPURE (Biorema) 260 HF (SA 2.6 m^2), in terms of IL-6 and PCT elimination while performing HF-HD versus HDF.

The BIOPURE (Biorema) 260 HF dialyzer used in this study resulted in an IL-6 RR of (32.48 ± 5.72%), with HF-HD, significantly lower than (44.92 ± 5.11%) with HDF (p<0.001). Countless studies tested dialyzers of different yet smaller surface areas using either HDF, HF-HD, or both.

For instance, in 2021, Quiroga et al., studied the removal of IL-6 in sixteen end-stage renal disease patients with corona virus disease 2019 (COVID-19) undergoing HF-HD using polymethyl methacrylate filter showed a reduction rate of interleukin-6 of 25.0 [17.5–53.2%].[13]

Another study was conducted by Murt et al., 2022, on 9 end-stage renal disease patients with COVID-19 performed high flux dialysis using a MCO filter, a total of 54 measurements were evaluated. The median and interquartile ranges (IQRs) of IL-6 levels were significantly higher in patients who died than survived patients 112.0 pg/mL [48.3–399.4 pg/mL] and 5.3 pg/mL [2.2–27.4 pg/mL], respectively (p< 0.001). In the comparison of changes in IL-6 levels with dialysis sessions, patients who survived had lower post-dialysis levels (median: 4.5 pg/mL; IQR: 2.2–7.6). However, IL-6 levels had a tendency to increase with dialysis sessions in patients who did not survive COVID-19 (median: 237.0 pg/mL; IQR: 53.8–418.2pg/mL).[14]

In contrast, Hung et al., 2022, performed a meta-analysis which included 328 patients. The meta-analysis demonstrated no significant difference in IL-6 serum levels after hemodialysis using a medium cut-off (MCO) polyarylethersulfone and polyvinylpyrrolidone blend membrane.[15]

Furthermore, Kandi et al., 2022, conducted a systematic review, included randomized and nonrandomized studies comparing MCO and high-flux membranes in adults (>18 years) receiving maintenance hemodialysis. Outcomes included solute removal (plasma clearance or dialysate quantization), reduction ratios, and predialysis serum concentrations for a range of prespecified large middle molecules. They identified 26 eligible studies (with 1883 patients). Medium cut-off dialysis reduced mRNA expression of tumor necrosis factor (TNF)-α and IL-6 in peripheral leukocytes by mean difference of 15% (95% CI, −19.6 to −10.4; moderate certainty) and −8.8% (95% CI, −10.2 to −7.4; moderate certainty), respectively.[16]

Another study, by Shutov et al., 2023 studied 31 patients on hemodialysis from March 1,

2020, to August 1, 2021, in Moscow clinics. Inclusion criteria for patients in the study were an adequate dialysis according to the quantify hemodialysis number(KT/V index) of ≥1.4, absence of an active inflammatory process or infections, age over 18 years, standard hemodialysis regimen of 3 times per week, at least 4 h, levels of IL-6, IL-8, and CRP above the reference values. Patients were transferred from hemodialysis performed using a standard polysulfone membrane to a polymethyl-methacrylate membrane (Filtryzer BK-2.1F). For dialysis treatment of patients, blood flow rates of 250–350 mL/min were used, and the flow rate of the dialysis solution was set at 500 mL/min. The control group consisted of 19 patients, with similar inclusion parameters, who continued their treatment with hemodialysis using a polysulfone membrane. The aim of the research was to study the effect of the dialysis membrane (Filtryzer BK-2.1F) on the level of inflammation in routine practice compared to a polysulfone membrane. Adverse events were monitored. By the end of the study, after 12 months, the levels of cytokines were significantly decreased only in patients who had treatment with polymethylmethacrylate membrane, starting from the third month of treatment, and became close to normal levels: IL-6 from 16.9 ± 8.0 to 8.5 ± 4.8 pg/mL ($p \leq$ 0.0001). However, values of inflammation markers did not change in the control group.[17]

Another study, by Fischer et al., 2022, included 144 children, of which 103 (61 HD, 42 HDF) completed 12-month follow-up. Circulating biomarkers of bone formation and resorption, inflammatory markers, fibroblast growth factor-23, and klotho were measured.

Inflammatory markers -6, TNF)-α, and high-sensitivity CRP were lower in HDF than in HD cohorts at baseline and at 12 months follow-up (p <0.001).[18]

Comparing the results of our study concerningIL-6 RR, with other similar studies, it is apparent that the removal of middle molecules is superior with dialyzers of larger surface areas and with HDF in contrast to HF-HD.

The BIOPURE (Biorema) 260 HF dialyzer used in this study results showed a statistically significant reduction in the mean procalcitonin level post-dialysis, as compared to pre-dialysis levels, in both HF-HD and HDF (p<0.001). Notably, HDF brought about a significantly higher procalcitonin RR (50.32 ± 3.94%) in contrast to HF-HD (41.80 ± 4.32%) (p<0.001).

Our study findings came in agreement with previous studies, indicated significant procalcitonin reduction in both high flux and HDF.

Sonikian et al., 2020, studied 25 stable HD /3, ages ranged 44-89years), dialyzed thrice weekly for 55(6-274) months with a dialysate flow rate of 700ml/min. Patients were classified in two groups. Group A included 10 patients on pre-dilution OL-HDF. Group B consisted of 15 patients on conventional HD with low-flux polysulfone membrane. Twenty normal subjects formed a control group. Serum CRP and PCT levels were measured in duplicate in the OL-HDF and HD groups before and at the end of mid-week dialysis sessions and also in the control group. Pre-Dialysis serum PCT values in the total patients were higher than those in the controls (0.8260, 9ng/ml vs 0.2960, 55ng/ml, p<0.001). Compared with the control group pre-D PCT values were higher in both A group (0.5260, 15ng/ml p<0.001) and B group (1.0161, 13 ng/ml p=0.006). There was no significant difference in pre-Dialysis serum PCT values between A and B groups (p=0.261). At the end of Dialysis session serum PCT values decreased in A group (0.3260, 11ng/ml p<0,001) and increased in B group (1.1261, 21 ng/ml-p=0.014).[19]

Furthermore, in the study by Elsayed et al., 2018, PCT serum levels were measured before and immediately after HD in 50 adult patients (25 treated with high-flux membranes and 25 with low-flux membranes), without history of concurrent infections. The baseline PCT levels before HD were higher than healthy control individuals. There was a significant decrease in PCT serum levels after HD session by high-flux membranes but not by low-flux membranes (high flux 0.54 ng/ml pre-HD vs. 0.26 ng/ml post-HD, p=0.001, whereas in low flux 0.50 ng/ml vs. 0.53 ng/ml, P=0.066.[9]

In addition, the study by Kubo et al.,2019, showed that PCT levels decreased significantly

after 4 h of HD therapy. The study included 123 HD patients, underwent 4 h HD therapy using four types of membranes, cellulose triacetate, polyacrylonitril, polyethersulfone, and polysulfone. PCT was removed by HD treatment using each type of membrane, but the PCT reduction rate was significantly higher with the polyethersulfone membrane than with polyacrylonitril and polysulfone membranes.[20]

The study by Mori et al., 2012 showed a 19% reduction of the PCT level following a single HD session. Although a high-flux membrane was used for HD in these two studies (by Kubo et al., and Mori et al.,), the membrane type was not reported. Therefore, the different PCT reduction rates following a single HD session between some studies would be affected at least in part by membrane type.[21]

Finally, one of the limitations of our study was the relatively small number of studied patients. Also, data collected for each patient were derived from a single session of each HF-HD and HDF.

In conclusion, the dialyzer BIOPURE (Biorema) 260 HF, with a SA 2.6 m^2, is remarkably efficient in eliminating IL-6 and procalcitonin especially with OL-HDF compared to HF-HD, with acceptable albumin loss in the spent dialysate.

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Author Contributions

The study's principal investigators were HE, KG, and HSH. HE & HM proposed the topic of this research and designed the study. AM and KG collected the data. All authors contributed to preparing the final draft of the manuscript, revised the manuscript, and critically reviewed the intellectual contents. In addition, they have all read and approved the final manuscript and are responsible for its accuracy and integrity.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval

The study protocol was reviewed and approved by the Research Ethics Committee of the Faculty of Medicine, Ain Shams University (FMASU MD 294/2020). This study was carried out following the principles of the Declaration of Helsinki and the ethics committee of the faculty of medicine of Ain Shams University (reference number; FWA 000017585).

Informed consent

An informed written consent was obtained from each study subject before included in the study.

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