An Observational Study of the Fresh Frozen Plasma: Red Blood Cell Ratio in Postpartum Hemorrhage

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BACKGROUND: Postpartum hemorrhage is the leading cause of maternal death worldwide. Recent data from trauma patients and patients with hemorrhagic shock have suggested that an increased fresh frozen plasma:red blood cell (FFP:RBC) ratio may be of benefit in massive bleeding. We addressed this issue in cases of severe postpartum hemorrhage.

METHODS: We reviewed data from all patients diagnosed with severe postpartum hemorrhage during a 4-year period (2006–2009). Patients who were treated with sulprostone and required transfusion within 6 hours of delivery were included in the study and were divided into 2 groups according to their response to sulprostone: bleeding controlled with sulprostone alone (sulprostone group) and bleeding requiring an additional advanced interventional procedure including arterial angiographic embolization and/or surgical procedures (arterial ligation, B-Lynch suture, or hysterectomy; intervention group). The requirement or no requirement for advanced procedures constituted the primary end point of the study. Propensity scoring was used to assess the effect of a high FFP:RBC ratio on bleeding control.

RESULTS: Among 12,226 deliveries during the study period, 142 (1.1%) were complicated by severe postpartum hemorrhage. Bleeding was controlled with sulprostone alone in 90 patients (63%). Advanced interventional procedures were required for 52 patients (37%). Forty-one patients were transfused with both RBCs and FFP. The FFP:RBC ratio increased over the study period ($P < 0.001$), from 1:1.8 at the start to 1:1.1 at the end of the study period. After propensity score modeling (inverse probability of treatment weighting), a high FFP:RBC ratio was associated with lower odds for advanced interventional procedures (odds ratio [95% confidence interval], 1.25 [1.07–1.47]; $P = 0.008$). There were no deaths, severe organ dysfunction, or other complications as a consequence of severe postpartum hemorrhage.

CONCLUSIONS: In this retrospective study, a higher FFP:RBC ratio was associated with a lower requirement for advanced interventional procedures in the setting of postpartum hemorrhage. The benefits of transfusion using a higher FFP:RBC ratio should be confirmed by randomized-controlled trials. (Anesth Analg 2013;116:155–61)

Postpartum hemorrhage (PPH) is one of the most frequent life-threatening complications of childbirth. It may occur without any predictive signs and symptoms, and often with no predisposing conditions.[1] PPH accounts for nearly one-quarter of all maternal deaths worldwide, with an estimated 125,000 deaths per year.[2,3] However, these deaths are generally avoidable.[4] The incidence of PPH has recently increased in several developed countries, including Canada, Australia, and the United States. It is a major public health issue in both developed and developing countries.[5,6]

Therapeutic strategies for the management of PPH are fairly standard.[7,8] Bleeding control by obstetric, surgical, and radiologic interventions can be life-saving, and is often associated with transfusion in case of massive and life-threatening bleeding. Recently, prohemostatic treatments, including tranexamic acid, fibrinogen concentrates, or recombinant factor VIIa, have created great interest.[9]

Data from patients with trauma or a ruptured abdominal aortic aneurysm suggest that higher fresh frozen plasma:red blood cell (FFP:RBC) ratios may contribute to better control of the lethal triad of acidosis, hypothermia, and coagulopathy, and ultimately lead to improved survival in severe hemorrhage.[10] To our knowledge, no data regarding the FFP:RBC ratio in obstetric hemorrhage have been published. The aim of this study was, therefore, to describe the effects of our new blood transfusion strategy increasing the FFP:RBC ratio, and to describe a possible association between an increased FFP:RBC ratio and better control of severe PPH at a single institution. Our hypothesis was that a higher FFP:RBC ratio would be associated with better and more rapid control of bleeding, consequently limiting the need for more aggressive surgical or radiologic interventions.

METHODS

We reviewed the data from all women who delivered after 24 weeks of gestation at Cochin Port-Royal, a Parisian

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tertiary university maternity unit, during a 4-year period (2006–2009). All parturients followed in our institution are informed that their medical data are recorded prospectively and saved on an exhaustive database, according to Commission Nationale de l'Informatique et des Libertés recommendations. Because this study was conducted on retrospective data collected from this database, informed or signed consent from each parturient was waived; the study was approved by the IRB from Bichat Hospital in Paris. In our unit, relevant data, including age, weight, height, gestation, parity, single or multiple pregnancy, vaginal, instrumental or cesarean delivery, type and insertion of the placenta, induction or augmentation of labor, use of epidural analgesia, postpartum complications, and neonatal variables are prospectively collected in a database (DIAM, 4D).

Patients with a PPH ≥500 mL are managed by manual uterine examination and/or removal of retained placenta, genital tract examination, and IV administration of oxytocin (20 U). In accordance with French practice guidelines, if these procedures are ineffective after 15 to 30 minutes, the patient is said to have severe PPH, and IV prostaglandin E_2, sulprostone, is administered (500 μg over 1 hour).[7,11] Blood hemoglobin level is measured with point-of-care testing, and blood samples are collected for assessment of hemoglobin concentration and coagulation in the hospital laboratory. Patients are transfused according to clinical evaluation of the severity of the bleeding as stated in European guidelines.[12] The decision to transfuse FFP is exclusively under the control of the anesthesiologists in our institution. This decision to transfuse blood products is based on the clinical situation and laboratory coagulation results. If sulprostone does not control bleeding, an advanced interventional procedure is performed, which may include arterial angiographic embolization and/or surgical procedures (arterial ligation, B-Lynch suture, or hysterectomy). During the study period, no antifibrinolytic drugs, such as tranexamic acid, were used, nor was fibrinogen concentrate administered. Compressive techniques, such as intrauterine balloons, were not used.

For the purposes of our study, we included all patients with PPH who received sulprostone and were transfused within the first 6 hours of delivery. Patients were divided into 2 groups according to the success or failure of hemorrhagic control with sulprostone: bleeding control achieved with sulprostone alone (sulprostone group) and bleeding control achieved only after an advanced interventional procedure (intervention group).

The electronic medical records of these patients were reviewed by anesthesiologists and obstetricians (VT, FG) to determine the presence of risk factors for PPH, and to identify the management of PPH and the use of blood component therapy. The primary analysis was to calculate the FFP:RBC ratio in the sulprostone group compared with the intervention group. A secondary analysis was conducted with the FFP:RBC ratio transformed as low versus high as the independent dichotomous variable, and the incidence of advanced interventional procedure as the dependent (primary outcome) variable. The "low-ratio" versus "high-ratio" cutoff for FFP:RBC was defined as ≤0.5. We chose this cutoff ratio because our clinical practice was to transfuse 1 U of FFP for every 2 U of packed RBCs at the beginning date of our study. This categorical analysis with the FFP:RBC ratio (low versus high) as the independent variable was conducted only for the patients who received FFP. The lowest values of hemoglobin, fibrinogen concentration, platelet counts, and longest prothrombin time were recorded for each patient.

Because there was no control on treatment allocation in the present study, we used a propensity score method to consider this bias. Among the various techniques using propensity score, we chose to use propensity score weighting, because it seemed the most appropriate method given the relatively small number of subjects.[13] We used the inverse probability of treatment weighting (IPTW) technique, where exposed and unexposed individuals are weighted to represent the population. The variables included in the propensity score model were the total number of RBCs transfused, the lowest values of fibrinogen concentration and platelet counts, the longest prothrombin time, and the year of inclusion. These 4 variables were chosen because they constitute validated significant markers of PPH severity.[1] The year of inclusion was also chosen because of changes observed over time in FFP transfusion. We evaluated the performance of the inverse probability of treatment weighting by assessing the means before and after weighting. We then assessed the effect of a high FFP:RBC ratio in the weighted sample using a generalized linear model. The odds ratio of success (i.e., no need for advanced interventional procedures) in patients who received a high FFP:RBC ratio was calculated (odds ratio [OR] [95% confidence interval {CI}]) after the IPTW technique.

Results are expressed as mean ± SD, median (range), or median (interquartile range). Association between single variables and outcome was assessed by a Student *t* test or a Wilcoxon rank sum test for quantitative variables, and Fisher exact test for categorical variables. Multiple secondary outcomes were reported for exploratory purposes only, and therefore, were not corrected for multiple comparisons. Multivariate analysis and propensity scoring were performed after univariate analysis. All tests were 2-sided, and $P < 0.05$ was considered significant.

RESULTS

During the 4-year period, 12,226 women delivered at Port-Royal Maternity, and 639 of them received sulprostone for PPH. Of these, 142 (22%) were transfused with RBCs within the first 6 hours after delivery and are the cohort for this study (Fig. 1). The leading cause of PPH was uterine atony (61%), followed by abnormal placental implantation (26%).

Bleeding was controlled with sulprostone alone in 90 of the 142 patients (sulprostone group), and 52 patients required advanced interventional procedures in the intervention group. There were no differences in sociodemographic or obstetric characteristics (except for parity) between the groups (Table 1). The FFP:RBC ratio increased significantly over the 4-year period (from 1:1.8 in 2006 to 1:1.1 in 2009; $P < 0.001$; Fig. 2).

In the propensity score analysis, we evaluated and subsequently confirmed the performance of the inverse probability of treatment weighting by assessing the means before and after weighting for the whole cohort, including

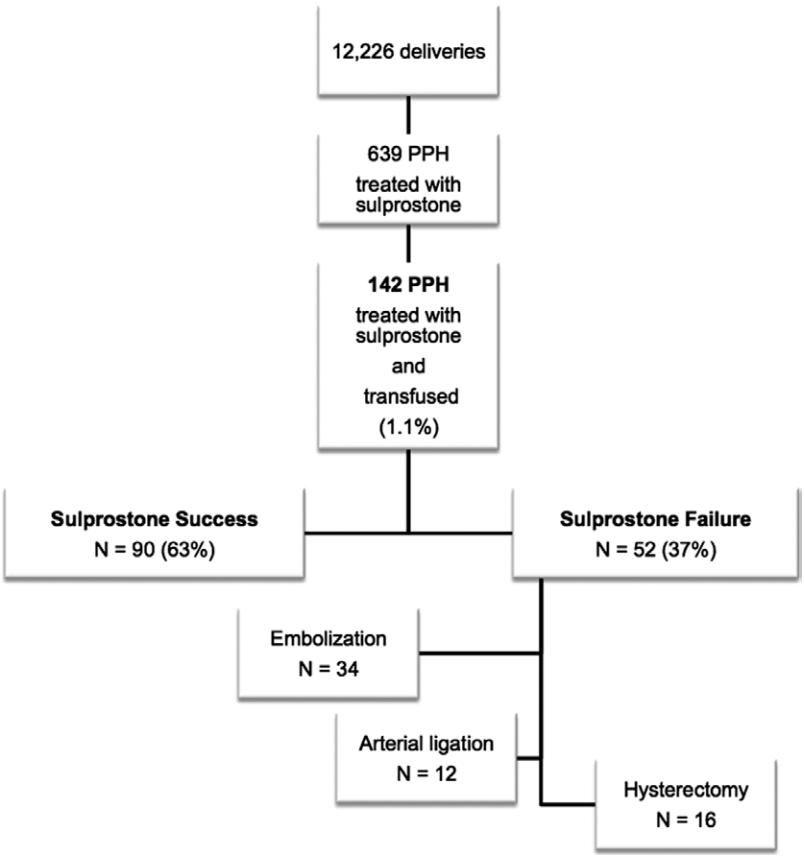

Figure 1. Study flow chart. PPH = postpartum hemorrhage.

patients who did not receive FFP, and for the 41 patients who received at least 1 U of FFP (Tables 2 and 3). Propensity score analysis demonstrated that a high FFP:RBC ratio was associated with fewer requirements for advanced interventional procedures (OR [95% CI], 1.25 [1.07–1.47]; $P = 0.008$) for the whole cohort, and for patients who received at least 1 U of FFP (OR [95% CI], 1.58 [1.19–2.10]; $P = 0.003$).

Table 1. Demographic, Obstetric, Anesthetic, and Hemorrhage Characteristics of Patients

	Sulprostone group, *n* = 52	Intervention group, *n* = 90	*P* value
Age (y)	32.6±5.9	33.7±4.9	0.26
Parity (*n*)			
Nullipara	53	20	0.02
Parous	37	32	
Pregnancy (*n*)			
Single	74	41	0.66
Multiple	16	11	
Gestational age (wk)	35±5	36±4	0.12
Mode of delivery			
Vaginal (spontaneous/ instrumental)	44 (24/20)	29 (15/14)	0.73
Cesarean (elective/ nonelective)	46 (10/36)	23 (7/16)	
Birth weight (g)	2481±1119	2783±988	0.10
Anesthesia			
Neuraxial	62	12	0.89
General	22	39	
Other	6	1	
PPH etiology			
Uterine atony	56	31	0.29
Placenta abruption	9	2	
Abnormal placentation	20	17	
Other	5	2	

Results are expressed as mean ± SD and counts.
PPH = postpartum hemorrhage.

The univariate analyses comparing the sulprostone to the intervention group are shown in Tables 4 and 5. The FFP:RBC ratio was significantly higher in the sulprostone group than in the intervention group (1:1.2 vs 1:1.6). Laboratory variables for women who received FFP compared with those who did not are shown in Table 6.

Of the 41 patients who received FFP and RBC transfusion, bleeding control was obtained with sulprostone only in 18 patients, whereas at least 1 additional procedure was required in the 23 others (10 embolizations, 8 arterial ligations, and 13 hysterectomies). No significant or clinical meaningful complications from blood transfusion were reported on the electronic records or medical files. No clinical deep vein thrombosis or maternal deaths occurred in either group.

DISCUSSION

To our knowledge, this study is the first to analyze the association between the FFP:RBC ratio and the outcome of severe PPH. Our results suggest a possible benefit of a higher FFP:RBC ratio in patients with severe PPH who require transfusion in massive continuous bleeding. A higher ratio was associated with more frequent success of sulprostone treatment to control bleeding, thus decreasing the need for advanced interventional procedures. Because there was no control on treatment allocation in the present

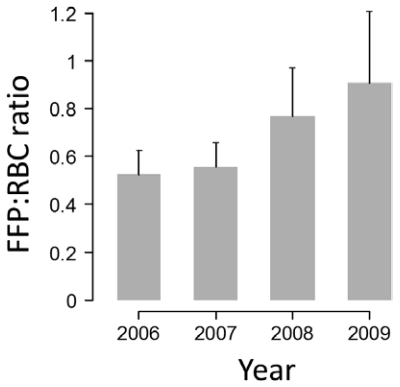

Figure 2. Trends in fresh frozen plasma:red blood cell (FFP:RBC) ratio (mean ± SD) over the 4-year study period (2006–2009) demonstrating a significant increase ($P < 0.001$, using analysis of variance).

study, one may argue that the patients receiving low or high FFP:RBC ratio were not comparable. We therefore used a propensity score method to account for this bias. This propensity score modeling demonstrated a significant association between the use of high FFP:RBC ratio and bleeding control without request for advanced interventional procedures. If the beneficial effects of a high, compared with low, FFP:RBC transfusion ratio are supported by well-controlled, randomized-controlled (yet difficult to perform) studies, this strategy could decrease total blood loss, limit the need for third-line surgical or radio-interventional treatments, and reduce maternal morbidity.

Recent studies in trauma and high-risk hemorrhagic surgery have suggested that a more liberal use of FFP may be beneficial in cases of massive bleeding.[10] Whereas guidelines conventionally recommend a 1:3 or even 1:2 FFP:RBC ratio, a growing trend toward a 1:1 ratio has emerged for combat casualties[14] or ruptured aortic aneurysm patients[15] receiving massive transfusions (>4 U RBCs in 1 hour or 10 U RBCs within 24 hours). A mathematical model of blood loss also supports this approach during hemorrhagic shock.[16] It is evident that parturients in hemorrhagic shock after delivery cannot be compared with young, healthy soldiers severely injured in the battlefield, or elderly patients with a ruptured abdominal aortic aneurysm. One may, however, argue that blood coagulation disorders can occur very early in cases of massive bleeding after delivery. By analogy with the early lethal triad of acidosis, hypothermia, and coagulopathy described in trauma patients, FFP transfusion might be required earlier and in larger amounts than has been generally recommended or used in cases of severe PPH.

From our current results, we suggest that the hypothesis of an additive effect of sulprostone and increased use of FFP in cases of severe PPH can be considered. Observational studies suggest the development of early coagulopathy in the setting of PPH.[17,18] Obstetric hemorrhage is often complicated by an acquired coagulopathy, because of dilution and/or consumption of clotting factors, mainly fibrinogen and platelets.[5,18] In addition, anemia contributes to impaired platelet responses.[19] Moreover, massive hemorrhage with hypovolemic shock causes tissue hypoxia, acidosis, hypothermia, and systemic inflammatory responses, which can trigger disseminated intravascular coagulation.[20] Several studies have established a strong relationship between a decreased fibrinogen level and the outcome of severe PPH.[21,22] Others have demonstrated or suggested the usefulness of strategies aimed at blood coagulation support with either fibrinogen[23,24] or prohemostatic agents in the management of PPH.[25,26] We did not use prohemostatic agents, although these should also be considered.

One aspect of this concept that needs further consideration is the optimal timing of FFP transfusion. Snyder et al.[27] suggested a temporal relationship between the FFP:RBC ratio and mortality in massively transfused trauma patients. These authors showed that a higher FFP:RBC ratio was associated with a lower mortality risk when the FFP:RBC ratio was considered a fixed value at 24 hours. However, this association was no longer statistically significant when the timing of the FFP transfusion was considered, thus demonstrating possible survivor bias. It is also possible that the actual FFP:RBC ratio may be less important than the timing of the administration of FFP.[28] Earlier administration compared with later administration of FFP

Table 2. Propensity Score Analysis in the Whole Cohort

	Unweighted			Weighted		
	Low ratio	High ratio	*P* value	Low ratio	High ratio	*P* value
Red blood cells (transfused units)	3.6±3.7	5.6±3.1	0.0045	5.5±6.3	3.9±2.3	0.42
Nadir platelets (giga/L)	145±78	91±49	<0.0001	124±82	136±55	0.61
Nadir fibrinogen (g/L)	2.6±1.1	1.2±0.9	<0.0001	2.2±1.2	2.4±1.2	0.66
Longest prothrombin time (s)	15.0±2.0	18.0±2.6	<0.0001	16.4±3.5	15.3±2.8	0.41

Transfusion, nadir platelets and fibrinogen, and longest prothrombin time (expressed as mean ± SD) before and after weighting on the inverse probability of treatment (in the whole cohort, including patients receiving no fresh frozen plasma).

Table 3. Propensity Score Analysis in the 41 Patients Transfused with At Least 1 U Fresh Frozen Plasma

	Unweighted			Weighted		
	Low ratio	High ratio	*P* value	Low ratio	High ratio	*P* value
Red blood cells (transfused units)	12.7±9.0	5.5±3.1	0.08	8.5±6.5	5.9±3.3	0.19
Nadir platelets (giga/L)	57±33	91±49	0.04	73±28	87±49	0.29
Nadir fibrinogen (g/L)	1.1±0.4	1.2±0.9	0.57	1.2±0.4	1.2±0.9	0.75
Longest prothrombin time (s)	18.4±2.9	18.0±2.6	0.72	17.4±2.5	18.0±2.6	0.52

Red blood cell transfusion, nadir platelets and fibrinogen, and longest prothrombin time (expressed as mean ± SD) before and after weighting on the inverse probability of treatment.

Table 4. Blood Component Transfusion and Fresh Frozen Plasma:Red Blood Cell Ratio (Whole Cohort)

	Sulprostone group, *n* = 90	Intervention group, *n* = 52	*P* value
Red blood cells (U)	3.1±2.9 2 (1)	5.3±4.1 4 (3)	<0.001
Fresh frozen plasma (U)	0.7±1.8 0 (0)	2.1±2.9 0 (0)	<0.001
Platelets (U)	0.04±0.25 0 (0)	0.32±0.85 0(0)	0.004
Nadir hemoglobin level (g/dL)	7.6±1.2	7.2±1.2	0.07
Nadir platelets level (giga/L)	157±85	106±53	<0.001
Longest prothrombin time (s)	15.1±2.6	18.8±5.5	<0.001
Nadir fibrinogen concentration (g/L)	2.7±1.2	1.7±1.1	<0.001

Data are presented as mean ± SD and median (interquartile range) values.

may be a possible strategy for correcting the coagulopathy accompanying massive bleeding, including in PPH.[29,30] Other transfusion strategies have also been described. For example, modeled on a system described by Riskin et al.[31] in the trauma service of the same hospital, Burtelow et al.[32] successfully applied a massive transfusion protocol in patients with obstetric hemorrhage. However, this and other similar protocols are currently not supported by data from randomized-controlled trials.

We are aware of the important limitations of this study. First, it is a single-center study. However, the advantage of a single-center study is that there is a unique and well-accepted protocol in place for PPH management.[7,11] The mean nadir hemoglobin concentration we observed indicates that guidelines were correctly followed in our unit. Moreover, our unit and hospital use exhaustive databases including transfusion data sets. Second, the study is retrospective, with potential severity bias. Performing a randomized study using FFP in the setting of severe life-threatening PPH would be complex. However, our results demonstrating a significant association between

Table 5. Blood Component Transfusion and Fresh Frozen Plasma:Red Blood Cell Ratio in the 41 Patients Transfused with Both Fresh Frozen Plasma and Red Blood Cell

	Sulprostone group, *n* = 18	Intervention group, *n* = 23	*P* value
Red blood cells (U)	5.0±5.9 4 (3)	8.2±4.5 6 (6)	0.05
Fresh frozen plasma (U)	3.6±2.5 3 (2)	4.9±2.5 4 (3)	0.12
Platelets (U)	0.1±0.5 0 (0)	0.7±1.1 0 (1)	0.06
Nadir hemoglobin level (g/dL)	7.0±1.0	7.3±1.1	0.36
Longest prothrombin time (s)	19.1±5.1	24.1±8.9	0.03
Nadir fibrinogen concentration (g/L)	1.6±0.9	0.8±0.5	0.001
Fresh frozen plasma:red blood cell ratio	0.86±0.27	0.62±0.21	0.003

Data are presented as mean ± SD and median (interquartile range) values.

Table 6. Blood Component Therapy in Patients Who Received Fresh Frozen Plasma Versus Those Who Did Not

	No FFP transfused, *n* = 101	FFP transfused, *n* = 41	*P* value
Red blood cells (U)	2.7±1.2 2 (1)	6.8±5.3 2 (4.5)	<0.001
FFP (U)	NA	4.3±2.5 3 (4)	—
Platelets (U)	0.01±0.1 0 (0)	0.49±0.98 0 (1)	<0.001
Nadir hemoglobin (g/dL)	7.6±1.2	7.2±1.1	0.06
Nadir platelets level (giga/L)	158±79	88±52	0.001
Longest prothrombin time (s)	14.9±2.2	21.7±7.2	<0.001
Nadir fibrinogen concentration (g/L)	2.7±1.1	1.1±0.8	<0.001

Results are expressed as means ± SD or medians [interquartile range].
FFP = Fresh frozen plasma; NA = not applicable.

high FFP:RBC ratio and bleeding control suggest that such a trial is justified. Third, the main end point of this study (success or failure of conservative therapy with sulprostone alone) is questionable. Indeed, the need for advanced radiologic or surgical treatment is not defined by internationally accepted and easily measurable bedside variables. Decisions regarding the failure of conservative therapy and the need for advanced radiologic or surgical treatment may, therefore, vary among centers or caregivers. Use of third-line advanced treatments may also depend on the availability of equipment or expertise in different centers. Fourth, no prospective measurement of adverse effects associated with transfusion was performed, and we cannot exclude that adverse effects may be more common with increased use of FFP, although major events are usually registered in our files or electronic medical records. Finally, we can only conclude an association and not causality.

Our results suggest that timely administration of FFP in predetermined quantities may be beneficial in the obstetric population in case of massive hemorrhage. However, well-controlled studies in obstetric patients are needed to confirm these results and to determine whether data from trauma patients can be extrapolated to obstetric hemorrhage. Blood product administration should never be viewed as innocuous.[33,34] Several studies have described a relationship between the FFP:RBC ratio and hospital-acquired infections, pneumonia, acute respiratory distress syndrome, transfusion-related acute lung injury, or multiorgan failure. Hence, individualized goal-directed hemostasis therapy should be encouraged.[9,35] Other techniques or devices, such as thromboelastography, may help assess PPH-associated coagulopathy more precisely and quickly, enabling earlier correction of abnormalities, and consequently reduce morbidity.

DISCLOSURES

Name: Pierre Pasquier, MD.
Contribution: This author helped design and conduct the study, analyze the data, and write the manuscript.

Attestation: Pierre Pasquier has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.
Name: Etienne Gayat, MD, PhD.
Contribution: This author helped analyze the data.
Attestation: Etienne Gayat has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
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