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Clinical and Laboratory Consequences of Platelet Transfusion in Shiga Toxin–Mediated Hemolytic Uremic Syndrome☆

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ABSTRACT

Recent studies suggest that platelet transfusions are harmful in patients with thrombotic thrombocytopenic purpura, an entity of thrombotic microangiopathies. As the typical or Shiga toxin–producing *Escherichia coli*–induced hemolytic uremic syndrome (STEC-HUS) is also classified as thrombotic microangiopathy, we complement these data with an analysis of 250 patients from the German O104:H4 STEC-HUS outbreak. The effect of platelet transfusion in 44 patients who received platelet transfusions vs 206 control patients was investigated. Criteria for both groups were severe thrombocytopenia less than 50/nL, severe hemolysis with administration of packed red blood cells, and a complicated clinical course with admission to intensive care units. Readouts were clinical complications and changes in routine clinical chemistry and whole blood count. Chemistry values at admission and demographic parameters were comparable. Platelet transfusions were administered in 44 cases a median of 7 (interquartile range, 6-9) days after diarrhea onset. After platelet transfusion, we observed a transient and slight increase in inflammation parameters. No significant difference in major complications such as seizures, or requirement for ventilation or renal replacement therapy could be observed. Thrombotic events such as thrombosis or embolism were comparably rare in both groups (2.3% in platelet transfused vs 4.4% in controls, P = not significant). The mortality was not significantly different (0% vs 2.6%, P = not significant) in our study cohort, but overall in the outbreak, 6 of 711 STEC-HUS patients in Germany died of a procedural-related bleeding complications. In conclusion, platelet transfusions seem comparably safe in adult STEC-HUS patients, considering both the possible necessity for invasive procedures and potential risk for severe bleeding.

Contents

☆ Conflicts of interest: None.

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An ongoing controversy discusses the safety of platelet transfusions in patients with platelet consumptive disorders as thrombotic microangiopathy, which is characterized by hemolytic anemia, thrombocytopenia, and multiorgan impairment [1]. Restricted use of platelet transfusions is reasoned by clinical case series and the pathophysiologic rationale that transfusions could contribute to arterial microthrombi and tissue ischemia [2]. In 2015, 2 retrospective studies of large national cohorts suggested that platelet transfusion were harmful in patients with thrombotic thrombocytopenic purpura [3,4]. These studies prompted us to investigate this matter in Shiga toxin–producing *Escherichia coli*–induced hemolytic uremic syndrome (STEC-HUS), another form of thrombotic microangiopathy. Although restricted use of platelet transfusion is recommended for STEC-HUS patients [5,6], only one study has analyzed the effect of platelet transfusion on clinical outcome [7]. In that analysis, no clear disadvantage was found investigating 24 children.

In the following article, we describe the experience of the German STEC-HUS outbreak caused by ingestion of Egyptian fenugreek sprouts contaminated with Shiga toxin–producing *E. coli* serovar O104:H4 in May to July 2011 [8]. Our consortium gathered a detailed clinical data set of 711 patients with HUS from the German O104:H4 STEC-HUS outbreak. Sixty-one of these patients had received platelet transfusions during the hospitalization. Focus was set short-term effects and striking adverse effects such as complications in platelet transfusions, arterial or venous thrombotic events, in-hospital mortality, bleeding complications, or increase of inflammatory parameters. Extensive chemistry values and precise dates for interventions and complications allowed for the investigation of timewise relation between platelet transfusion and adverse effects.

Methods

Patients

Analyses were restricted to patients who had severe thrombocytopenia with platelet count of 50/nL or lower. To adjust the subgroups, further mandatory criteria were the admission to intensive care units (ICU) as indicator for severe clinical affliction and the transfusion of red blood cell (RBC) concentrates as a marker for extensive hemolysis. With these restrictions applied, 44 patients who received platelet transfusions within the first 14 days after onset of diarrhea were compared with 206 control patients without platelet transfusions. Some patients received platelets but were excluded from both groups because their data were incomplete (16 patients). In one case, the transfusion was related to secondary complications after the acute phase of STEC-HUS.

The HUS diagnosis was established by the treating physician. For the present analysis, we retrospectively collected demographic, clinical, laboratory, and information on hospital course and medication on a standardized case-history form by a dedicated study team. The extracted data were imported into a database. Data were checked for correctness, consistency, and plausibility by a second investigator.

Statistical Evaluation

Data are presented as total (n [%]) or median and interquartile range. Comparisons were calculated by Student *t* test as numeric value, “not

Table
Baseline parameters, clinical complications, and interventions for 711 STEC-HUS patients

	Platelet transfusion (n = 44)	Controls (n = 206)	*P*	All nonincluded patients (n = 667)	*P*
Baseline characteristics					
Age (y)	37.5 (5-78)	44 (9-83)	n.s.	41 (27.3-58)	n.s.
Sex female, n (%)	36 (81.8)	153 (74.3)	n.s.	470 (70.5)	n.s.
BMI admission (kg/m^2)	22.6 (20.3-24.8)	23.4 (20.8-26.4)	n.s.	23.7 (21.3-26.4)	n.s.
Platelet count at admission (/nL)	81 (43.3-222.1)	89 (37.4-218)	n.s.	99.7 (41.4-222.3)	n.s.
Hemoglobin at admission (g/dL)	12.3 (10.2-13.9)	12.8 (10.2-14.3)	n.s.	12.2 (10.4-14)	n.s.
LDH at admission (U/L)	680 (221.8-1244)	596 (196.9-1295.8)	n.s.	548.2 (205-1182.3)	n.s.
Creatinine at admission (μmol/L)	113.8 (66.5-217)	119 (71-306.5)	n.s.	119 (71-252)	n.s.
Therapy					
Platelet transfusion, n (%)	44 (100)	0 (0)	n.a.	17 (2.5)	<.001
Platelets on day of transfusion (/nL)	23.5 (14-32.3)		n.a.	23 (17-45)	n.s.
Day of first platelet transfusion	7 (5-9)		n.a.	7.5 (7-9)	n.s.
Count of platelet transfusions	2.1 ± 1.3		n.a.	2 (1-2.3)	n.s.
Clinical course					
Day of lowest platelet count	7 (6-8.3)	7 (5-9)	n.s.	8 (6-10)	n.s.
First day of platelets <50/nL	6 (4-6.5)	6 (4-7.5)	n.s.	6 (5-8)	n.s.
Minimal platelet count (/nL)	23.5 (14-32.3)	24 (18-34)	n.s.	33 (21-54)	<.001
Minimal hemoglobin (g/dL)	6.2 (5.6-6.7)	6.1 (5.6-6.7)	n.s.	6.7 (6-7.8)	<.001
Maximal LDH (U/L)	1759 (1401.8-2185)	1521 (1154-1990)	n.s.	1242 (747-1858.5)	.003
Maximal creatinine (μmol/L)	392.5 (257.3-602.5)	469 (273.5-652.5)	n.s.	318 (155-566)	n.s.
Maximal leukocyte count	19.6 (15.6-28.9)	20 (14.7-26)	n.s.	16.5 (5.7-111)	<.001
ICU, n (%)	44 (100)	206 (100)	n.a.	331 (53)	<.001
Day of ICU admission	6 (5-8)	8 (5-11)	.022	8 (5-11)	.013
Duration for ICU (d)	12 (7-21)	11 (5-20)	n.s.	10 (4-18)	n.s.
Dialysis, n (%)	38 (86.4)	165 (80.1)	n.s.	391 (58.6)	<.001
Blood transfusion, n (%)	44 (100)	206 (100)	n.a.	423 (64.7)	<.001
No. of RBC transfused	8 (6-10)	4 (2-8)	<.001	4 (2-6)	<.001
Ventilation, n (%)	21 (48.8)	86 (42.6)	n.s.	132 (21.5)	<.001
Seizures, n (%)	15 (35.7)	70 (34.8)	n.s.	114 (17.6)	.003
Death, n (%)	0 (0)	6 (2.9)	n.s.	18 (2.7)	n.s.
Day of decease		16 (15-18)	n.a.	16 (10-27)	n.a.
Eculizumab, n (%)	28 (63.6)	115 (56.1)	n.s.	251 (38)	<.001
Plasma exchange, n (%)	42 (95.5)	196 (95.1)	n.s.	510 (76.5)	.004

Platelet-transfused patients meeting the inclusion criteria (n = 44) are compared both to the control group (n = 206) and all other patients (n = 667, including the control group). Seventeen patients with platelet tranfusion were excluded from both intervention and control groups because they either provided insufficient data or, in some cases, received transfusion long after the acute phase of STEC-HUS. n.a., not available; n.s., not significant
Abbreviations: BMI, body mass index; n.a., not available; n.s., not significant.

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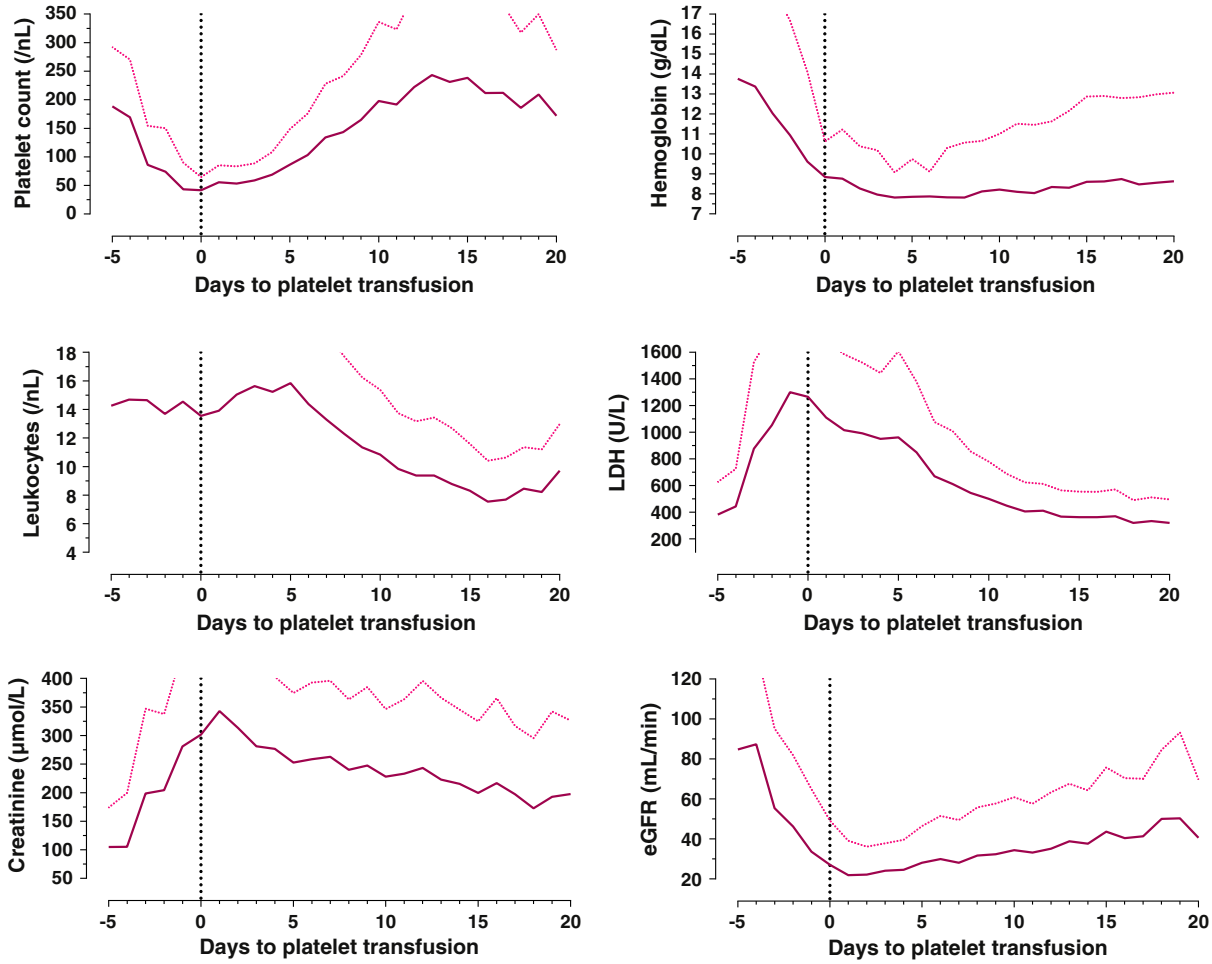

Fig 1. Course of blood count and chemistry values for patients with day of first platelet transfusion set as day zero. Dotted line marks the first day of platelet transfusions as day zero.

significant" for all values greater than .05, or "not available." Figures were created with Prism 6.0 by GraphPad Software, San Diego, California.

Ethical Approval

All the investigations and tests described were approved by the ethical committee of the Medical School Hannover (No. 1123-2011), the University of Lübeck (No. 11-103), University of Kiel (No. AZ A156/03), and University Hospital of Hamburg (PV3975).

Results

Patients having received platelet transfusions were predominantly female (n = 36; 81.8%) aged 38 (30-56) years including 3 children aged 5 to 18 years. Medical condition including comorbidities as hypertension (14% vs 19.7%, P = not significant), renal insufficiency (0% vs 1%, P = not significant), coronary heart disease (0% vs 2.6%, P = not significant), diabetes mellitus (4.7% vs 5.2%, P = not significant), or pregnancy (2.3% vs 3.2%, P = not significant) as well as body mass index (22.6 vs 23.4, P = not significant) were well comparable in both groups. Laboratory data at admission included a platelet count of 81 (43-222)/nL, hemoglobin levels of 12.3 (10.2-13.9) g/dL, lactate dehydrogenase [LDH] of 680 (222-1244) U/L, and creatinine levels of 114 (67-217) µmol/L and were well comparable to the control group without any significant differences.

Within 6 days (4-7 vs 4-8 days, P = not significant), platelet counts in patients dropped below 50/nL. The overall nadir of platelet count was reached shortly after (day 7 [6-8] vs day 7 [5-9], P = not significant) with comparable platelet counts of 24/nL (24 [14-32] vs 24 [18-34]/nL)). Platelet transfusions were administered on day 7 (5-9) after onset of diarrhea with 2 (1-2; average 2.1 ± 1.3) units. Lowest platelet counts on the date of transfusion or 1 day prior were 26 (18-34)/nL with at least 20 patients at 20/nL or lower.

Packed RBCs were first administered on day 7 (6-9) in the platelet transfusion group and on day 9 (7-12) in controls. Patients receiving platelets had a higher count of RBC than did controls (8 [6-10] vs 4 [2-8], $P < .001$).

Overall incidence of renal replacement therapy, mechanical ventilation, focal seizures, or death did not differ between transfused patients and controls (Table). Overall hospitalization time was longer by a median of 5 days (33 [21-42] vs 28 [22-36], $P = .041$) in transfused patients, and admission to ICUs was earlier at day 6 (5-8) vs 8 (5-11; $P = .025$) in transfusion patients. Thrombotic events such as thrombosis or embolism were comparably rare in both groups (2.3% vs 4.4%, P = not significant).

The effect on blood count and chemistry parameters was investigated. Projecting such parameters to the day of the first platelet transfusion as day zero and assessing the impact of intervention on the course of values (Fig 1), we recognized associated changes. Platelet count expectedly increased from 26 (18-34)/nL to 52 (39-76)/nL 1 day after transfusion, and similarly, hemoglobin levels increased due to the almost

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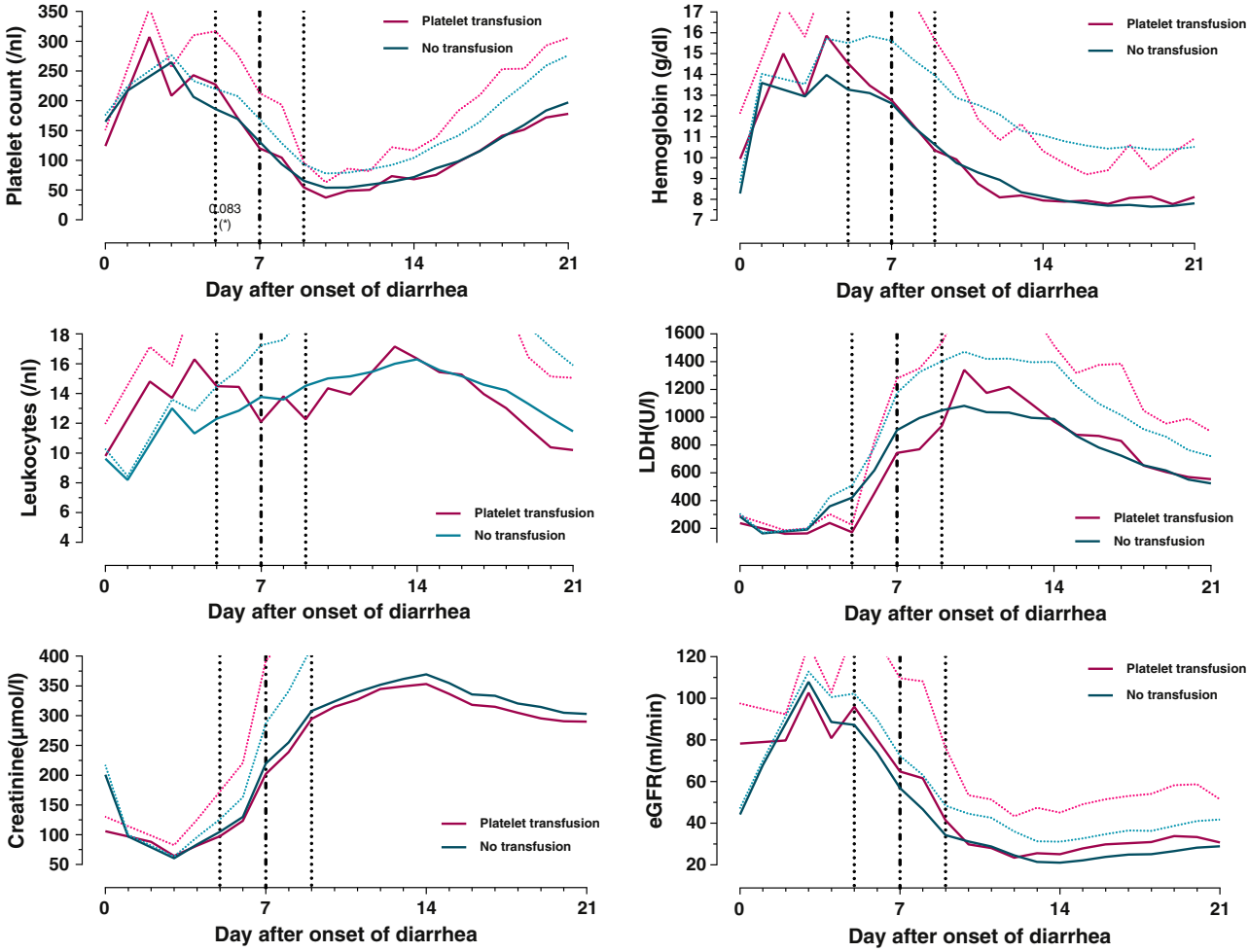

Fig 2. Course of blood count and chemistry values for platelet-transfused patients and controls with day of diarrhea onset as day zero. Dotted lines represent interquartile range and median of first platelet transfusion.

simultaneously administered RBC transfusion. Two days after transfusion, leukocytes, LDH, and creatinine presented consecutively elevated values for 3 to 5 days. Comparing the course of these to our control patients (Fig 2), platelet count, hemoglobin levels, and creatinine did not appear strikingly differing.

Discussion

Inclusion criteria for intervention and control groups restricted the analysis to the acute phase of STEC-HUS and provided solid comparability in baseline parameters. Age, sex, comorbidities, and chemistry values at baseline were well comparable (Table). Both for major complications of interventional procedures and for chemistry values, the first week after onset of diarrhea appear analogous (Figs 2 and 3). For no single day, values were significantly differing or tending to do so.

A possible link between the onset of complications and the first administration of platelet transfusions was assessed. Comparing each major end point with focus on the main time frame of platelet transfusion, we found that no increment in transfused patients was apparent (Fig 3). Overall, we did not find any association of platelet transfusion and clinical complications specific for STEC-HUS. However, regular complications of transfusions have to be taken into account. The necessity for advanced therapeutic intervention although might have supported the ambivalently discussed decision for platelet transfusion. The occurrence of seizures, mechanical ventilation, hemodialysis, and RBC transfusion was often followed by platelet transfusion (Supplementary Fig S1 in the online version at http://dx.doi.org/10.1016/j.tmrv.2016.06.004). Still, none of these appeared more frequent in platelet-transfused patients.

A slight increase of inflammation parameters cannot safely be negated because LDH levels and leukocyte count, both markers for a worse outcome of STEC-HUS [8], might slightly increase after platelet administration. This suggests that platelet infusion could enhance or prolong the activity of STEC-HUS by a minor amount.

A limitation of this study is that patients with STEC-HUS are more commonly children. The German outbreak 2011 primarily afflicted adults, and the administration of both platelet transfusion and interventional therapy would be considered more restrictively in children. Despite the potential adverse effect regarding inflammatory parameters, it must be emphasized that during the STEC-HUS epidemic, 6 of 711 patients die of bleeding complications after central catheter placement ($n = 4$), intubation ($n = 1$), and tracheotomy ($n = 1$).

In summary, a slight increment of inflammatory chemistry parameters is indicated by these data. However, no significant impact on hard outcome parameters in our patients could be observed. These data suggest that platelet transfusions should not be considered to be contraindicated for the treatment of bleeding or in advance of invasive procedures in STEC-patients with HUS.

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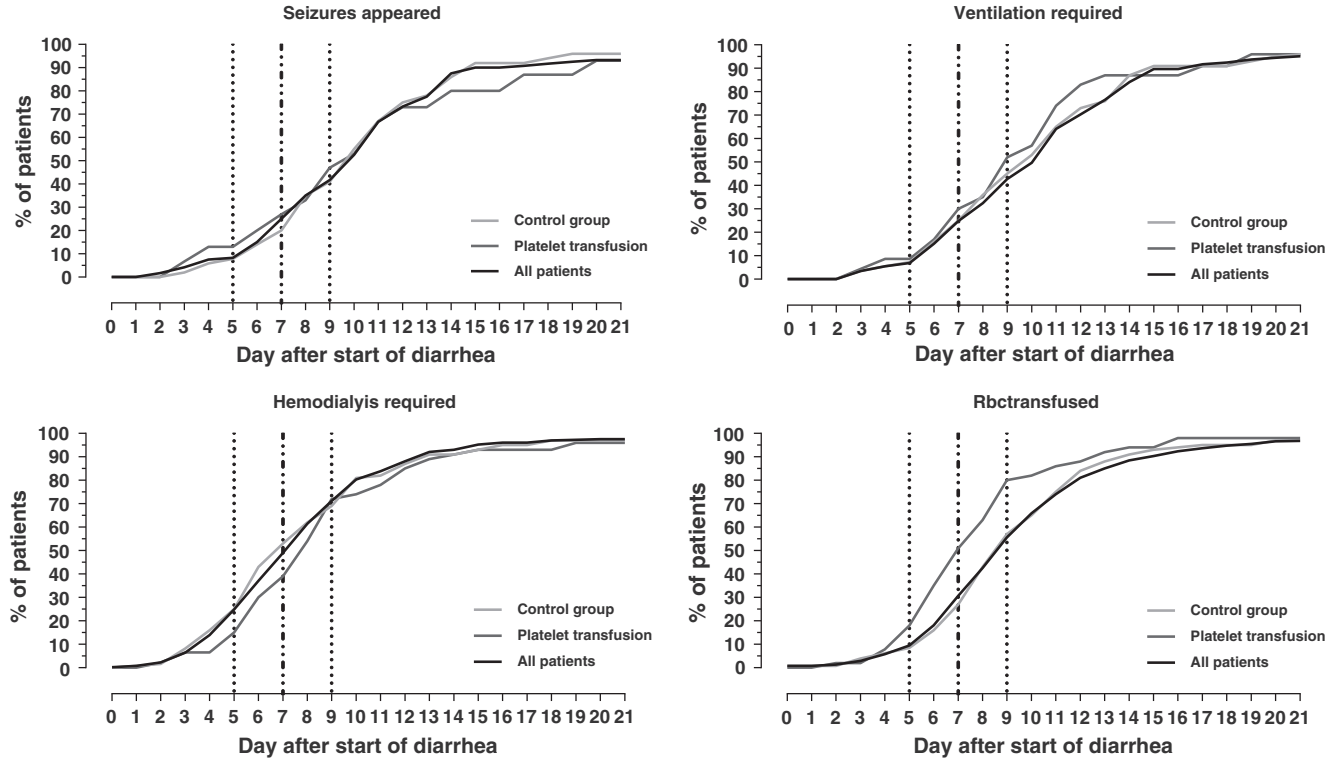

Fig 3. Restricted to patients with clinical complications or of interventional therapy. Platelet-transfused patients are shown in comparison to both controls and all patients not meeting the inclusion and transfusion protocol. Vertical lines represent interquartile range and median of first platelet transfusion.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.tmrv.2016.06.004.

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