Imported *Plasmodium vivax* malaria with severe thrombocytopenia: can it be severe malaria or not?

Spinello Antinori¹*, Alberto Corona², Anna Lisa Ridolfo¹, Laura Galimberti¹, Davide Ricaboni¹, Laura Milazzo¹ and Mario Corbellino¹

**Abstract**

**Background:** Thrombocytopenia is the most frequent malaria-associated hematologic alteration observed with all five *Plasmodium* parasites causing disease in humans. Although not included in the World Health Organization criteria for severe *Plasmodium falciparum* malaria, severe thrombocytopenia has been increasingly mentioned as an indicator of *P. vivax* malaria severity.

**Case:** Here, it is described a case of imported *P. vivax* malaria in a 37-year old man from Pakistan who presented with severe thrombocytopenia (5 × 10⁹/L). He was admitted to the intensive care unit and initially treated with a 1-day course of intravenous quinine followed by oral chloroquine and primaquine. The patient’s platelet count increased as early as 4 hours after treatment inception and the clinical course was favourable and uneventful.

**Discussion:** This case report, along with a review of published cases focusing on the relationship between thrombocytopenia and severe *P. vivax* malaria, suggests that the prognostic role of severe thrombocytopenia is ambiguous in absence of severe hemorrhagic complications and its use as diagnostic criterion of malaria severity may lead to overestimation of severe *P. vivax* malaria cases.

**Conclusion:** Due to the lack of high quality studies it is at present unclear if severe thrombocytopenia in the setting of *P. vivax* malaria should be considered indicative of severe malaria.

**Keywords:** *Plasmodium vivax*, Severe thrombocytopenia, Severe malaria, Imported malaria, Bleeding
and it has not as yet been validated as an independent severity parameter in vivax malaria. Of note, in several studies and case reports, severe thrombocytopaenia was described as the most prevalent severity sign of vivax malaria [11–15]. Therefore, it cannot be excluded that the use of such an indicator may lead to an overestimation of P. vivax malaria severity.

Here, it is described a case of imported P. vivax malaria characterized by severe thrombocytopaenia along with a review of similar cases reported in the literature. Furthermore, it is discussed whether severe thrombocytopaenia should be considered a reliable biomarker of P. vivax malaria severity.

Case report
A 37-year old male from Pakistan arrived in Italy in July 2013 to attend a professional course. After few days, he developed high grade fever (40 °C) associated with chills, headache and one episode of vomiting. He was visited by a primary physician who prescribed him cefixime 400 mg/day and acetaminophen. After 4 days, due to the persistence of fever and the onset of productive cough and asthenia, cefixime was changed to levofloxacin (500 mg/day). However, the fever did not resolve, and therefore the patient was taken to the nearest emergency department (ED). At presentation, he was febrile (39.5 °C), tachycardic (121 beats per min) and hypotensive (90/50 mm Hg); there were no meningeal signs and the Glasgow Coma Score was normal (15). Oxygen saturation while breathing ambient air was 99 %, the respiratory examination and a chest radiograph were both normal. Laboratory investigations were as follows: haemoglobin, 15.9 g/dL; red blood cell count, 5.54 × 10¹²/L; total white cell count, 6.3 × 10⁹/L (with 85 % neutrophils, 11 % lymphocytes and 4 % monocytes); platelet count, 14 × 10⁹/L. With the exception of P-dimer concentration (9376 ng/dL), the other coagulation parameters were within the normal range. Hypoaesthesia (127 mmol/L) was present as well as raised values of C reactive protein (126 mg/L), total bilirubin (3.3 mg/dL), and lactate dehydrogenase (371 U/L). Serum concentrations of glucose, liver enzymes, urea and creatinine were within normal ranges. An ultrasound scan of the abdomen showed no hepatosplenomegaly and a normal biliary tract. Legionella and pneumococcus urine antigens were negative. A thin blood film showed "malaria parasites" that were not identified at the species level by the laboratory technician. Due to lack of anti-malarial drugs and the expertise for the diagnosis and therapy of malaria, the ED physician contacted the Luigi Sacco hospital in Milan for assistance. Ten hours after presentation at the first ED, the patient was finally admitted to the intensive care unit of Luigi Sacco hospital with a provisional diagnosis of "severe malaria", based on the results of the laboratory tests (severe thrombocytopenia and raised bilirubin levels) and the presence of hypotension. On physical examination, when admitted to the ICU, the patient was conscious, fully oriented to time and place with high fever (40 °C) and had severe headache. The pulmonary, cardiovascular and abdominal examinations were reportedly unremarkable. Neither signs of bleeding nor skin petechiae were detected. No previous history of malaria episodes was elicited and no underlying chronic diseases were present. The patient was treated with a loading dose of intravenous quinine (1200 mg). At treatment inception the platelet count was 5 × 10⁹/L, without haemorrhagic manifestations. Examination of the peripheral blood smear by the haematologist did not reveal platelet clumping and a blood sample obtained with sodium citrate confirmed the finding of low platelet counts thus excluding a diagnosis of pseudothrombocytopenia. In the absence of bleeding the haematologist judged as unnecessary the use of platelet transfusions. Thick and thin blood smear examinations were diagnostic for P. vivax infection with schizonts, gametocytes and ring forms being detected and a very low parasitaemia (0.1 %). Plasmodium vivax monoinfection was subsequently confirmed by DNA polymerase chain reaction performed on a stored blood sample obtained on admission. Blood and urine cultures were obtained but gave negative results. Serology for HIV, CMV, dengue virus, leptospirosis, syphilis, Brucella and typhoid fever were negative.

Platelet counts showed a rapid increase soon after the infusion of quinine (i.e., 13 × 10⁹/L, 16 × 10⁹/L, 20 × 10⁹/L, 32 × 10⁹/L, respectively, after 4, 10, 18 and 24 h). The following morning an infectious diseases consultation was requested which suggested an interruption of intravenous quinine (after two doses administered). In consideration of the stable clinical condition and the diagnosis of P. vivax malaria the patient was transferred to the Infectious Diseases ward where oral chloroquine was started to complete the treatment. Parasite clearance was observed within 48 h after hospital admission as well as improvement or complete disappearance of all accompanying signs and symptoms (fever, headache, nausea, asthenia, myalgia). After completing a 3-day course of chloroquine treatment, and documentation of normal glucose 6-phosphate dehydrogenase activity levels, the patient was started on oral primaquine (15 mg of base in a 263 mg tablet per day for 14 days) and discharged the fifth day of hospitalization in good clinical conditions and with platelet counts within the normal range (223 × 10⁹/L).

Discussion
In this case report, a man from Pakistan with imported P. vivax malaria was initially classified as affected by severe
malaria and admitted to the ICU on the basis of profound thrombocytopaenia. Despite the initial presentation, the patient’s clinical course was uneventful and the platelet counts recovered very rapidly under anti-malarial treatment [16]. In recent years, an increasing number of case reports and hospital-based studies, have questioned the notion of “benign tertian malaria” by describing severe and even fatal malaria associated with P. vivax infection [3–8, 12–15]. In many instances, severe thrombocytopaenia was used by the authors of these reports as the stand-alone criterion of malaria severity, irrespective of the presence of haemorrhagic events and/or other signs of disease severity.

However, two relevant aspects deserve to be considered when interpreting the findings of these studies. The first concerns the lack of any specific case definition for severe P. vivax malaria and, consequently, the question of whether severe thrombocytopaenia should be considered, in the absence of bleeding, a marker of disease severity.

Thrombocytopaenia (i.e., a platelet count below 150,000/μL) is a frequent haematological finding in all types of malaria and it is observed in 29–93.3 % of patients with P. vivax malaria [9, 17]. The exact mechanisms underlying the decrease in platelet counts is still unknown, but various hypothesis have been advanced including immune-mediated phenomena, oxidative stress, alterations in splenic function and a direct interaction between the parasite and platelets [18–22]. Recently, Coelho and coworkers demonstrated that macrophage-driven phagocytosis of platelets may be an important contributory mechanism and that the mean platelet volume was greater in thrombocytopaenic patients with vivax malaria than in controls [23]. The latter finding is particularly interesting because the presence of large circulating platelets and may be viewed as compensatory mechanism in order to preserve primary haemostasis. Accordingly, bleeding is seldomly observed in the course of malaria even among patients with severe thrombocytopaenia. So what is the clinical and prognostic significance of severe thrombocytopaenia in patients with vivax malaria?

Thirty-three case reports of severe thrombocytopaenia (median platelet count: 21,000/μL, range: 2000–45,000/μL) in patients with vivax malaria have been published in the medical literature from 1993 to 2014 (the majority after 2006) [11, 12, 15, 24–51]. Ten individuals presented with haemorrhagic manifestations [27, 28, 30, 35, 38, 40, 41, 43, 48] and nine received platelet transfusions: all patients recovered with the exception of one who died because of shock and pancreatitis [45] (Table 1).

Information regarding the relationship between vivax malaria and thrombocytopaenia adopted as a criterion for assessing malaria severity may be also extracted from 17 clinical studies (13 from India [13, 14, 52–62], two from Pakistan [63, 64] and one each from Colombia and Sudan [65, 66]). In fifteen of these studies, a cut-off value of less than 50,000 platelets per μL was used to define severe thrombocytopaenia [13, 52–60, 62–66]. Overall, platelet counts below 50,000/μL were present in 335 out of the 906 cases of severe malaria examined (36.9 %), although the prevalence varied significantly among the studies, from 12.5 % to 93 % (Table 2), because of the different selection criteria employed. Bleeding manifestations (mainly epistaxis) were observed in 108 patients (34.8 %), but only in two patients were they serious enough to directly contribute to death (i.e., disseminated intravascular coagulation and gastrointestinal tract haemorrhage) [54, 58].

It is noteworthy that mixed P. vivax and P. falciparum infections were not ruled out in 14 out of 17 studies [14, 52, 53, 63–66]. In addition, coexisting infections that may contribute to thrombocytopaenia (such as dengue fever, leptospirosis or bacterial sepsis) were not excluded in the majority of the studies [14, 52–55, 57, 58, 60–66].

Regarding the latter issue, a recent study conducted in the Brazilian Amazon showed that 17.6 % of patients with P. vivax malaria had concomitant dengue infection and these had a higher probability to present with haemorrhagic manifestations and jaundice [67].

Other studies have focused on the prognostic role of thrombocytopaenia in vivax malaria. Leal-Santos and coworkers in a cross-sectional study conducted in 186 patients from the Mato Grosso region showed that mean platelet volume and platelet distribution width (PDW) were significantly associated with the presence of warning signs of severe and complicated malaria (i.e., anaemia, hypotension and elevated creatinine levels) with odds ratios (OR) of 3.47 and 5.44, respectively [68].

In keeping with the above mentioned results, a large study conducted in Papua New Guinea showed that the greatest risk of severe thrombocytopaenia was associated with P. falciparum malaria (OR 6.03 vs 3.73 for P. vivax). However, the mortality risk for patients with severe thrombocytopaenia was higher among patients without malaria (7.9 %) than among those with P. falciparum (2.1 %) or P. vivax (1.5 %) malaria [69]. The authors also found a 16-fold higher risk of death when severe thrombocytopaenia was associated with severe anaemia (haemoglobin concentration below 5 mg/dL), and concluded that severe thrombocytopaenia should serve as a warning sign of poor outcome in patients with malaria particularly when it is accompanied by severe anaemia. Based on their findings, Lampah and coworkers proposed a threshold of ≤20,000 platelets/μL as a defining severity criterion for both P. falciparum and P. vivax malaria [69].
Table 1 Published case reports of severe thrombocytopenia associated with severe *Plasmodium vivax* malaria

| Year of publication/reference | Location of malaria acquisition | Age/sex | Platelet count/μL (nadir) | Other complications | Diagnostic method/parasite density | P. falciparum excluded | Treatment/platelets transfusion (N unit) | Outcome |
|-----------------------------|---------------------------------|---------|---------------------------|---------------------|----------------------------------|----------------------|----------------------------------------|---------|
| 1997/[15]                  | Thailand                         | 27/F    | 22,000                    | No                  | Microscopy/serology/0.6 %       | Yes                  | Sulfadoxine-pyrimethamine + primaquine/no Chloroquine + primaquine/no | Recovery |
| 1998/[24]                  | India                            | 20/M    | 14,000                    | Severe anemia (Hb 3 g/dL) | Microscopy/NR                  | No                   | Chloroquine + primaquine/no            | Recovery |
| 1999/[11]                  | India                            | 43/F    | 5,000                     | No                  | Microscopy/RDT/NR               | Yes                  | Chloroquine + primaquine/no            | Recovery |
| 1999/[11]                  | Colombia                         | 32/M    | 17,000                    | Shock, ARDS         | Microscopy/PCR/5 %              | Yes                  | Quinine + primaquine/no                | Recovery |
| 2002/[12]                  | India                            | 43/M    | 8,000                     | No                  | Microscopy/RTD/NR               | Yes                  | Chloroquine + primaquine/no            | Recovery |
| 2003/[26]                  | India                            | 29/M    | 35,000                    | Jaundice            | Microscopy/PCR/<1 %              | Yes                  | Chloroquine + primaquine/no            | Recovery |
| 2003/[27]                  | Mexico                           | 30/M    | 6,000                     | Epistaxis           | Microscopy/NR                   | No                   | Quinine + doxycycline switched to chloroquine + primaquine/yes (20 units) | Recovery |
| 2004/[28]                  | Brazil                           | 20/M    | 2,000                     | Petechiae, hemorrhagic bullae | Microscopy/PCR/NR              | Yes                  | Chloroquine/yes (1 unit)/prednisone | Recovery |
| 2005/[29]                  | Brazil                           | 43/F    | 17,000                    | ARDS, shock         | Microscopy/RDT/NR               | Yes                  | Chloroquine + artesether + primaquine/No Chloroquine (1 dose) followed by quinine dihydrochloride + primaquine/yes (2 units)/steroids | Recovery |
| 2005/[30]                  | India                            | 7/M     | 6,000                     | Petechial rash, gum bleeding | Microscopy/bone marrow/NR      | No                   | Chloroquine + doxycycline switched to intravenous quinidine/yes (1 unit) | Recovery |
| 2006/[31]                  | Venezuela                        | 50/F    | 25,000                    | ARDS                | Microscopy/PCR/1200/μL          | Yes                  | Mefloquine + primaquine/no            | Recovery |
| 2006/[32]                  | Turkey                           | 22 days/F | 17,000            | Jaundice            | Microscopy/NR                   | No                   | Chloroquine + primaquine/yes (NR)    | Recovery |
| 2007/[33]                  | Guyana                           | 59/M    | 10,000                    | ARDS, shock; renal failure | Microscopy/PCR/5 %             | Yes                  | Quinine sulphate + doxycycline switched to intravenous quinidine/yes (1 unit) | Recovery |
| 2007/[34]                  | Pakistan                         | 59/M    | 39,000                    | ARDS, renal failure | Microscopy/RDT/PCR/3 %          | Yes                  | Chloroquine + primaquine/no            | Recovery |
| 2007/[35]                  | India                            | 8/M     | 20,000                    | Renal failure; petechial rash | Microscopy/RDT/24,000/μL       | Yes                  | Quinine dihydrochloride/no            | Recovery |
| 2007/[36]                  | Republic of Korea               | 21/M    | 25,000                    | Shock               | Microscopy/RDT/PCR/2352/μL      | Yes                  | Chloroquine + primaquine/no            | Recovery |
| 2007/[36]                  | Republic of Korea               | 33/M    | 40,000                    | Shock               | Microscopy/RDT/12,376/μL        | Yes                  | Chloroquine + primaquine/no            | Recovery |
| 2008/[37]                  | Brazil                           | 14/M    | 6,000                     | Shock; bleeding; increased liver enzymes (AST 1080 U/L) | Microscopy/bone marrow/PCR/NR | No                   | Chloroquine + primaquine/no            | Recovery |
| 2009/[38]                  | India                            | 4/F     | 11,000                    | Myocarditis         | Microscopy/PCR/6990/μL          | Yes                  | Artesunate + mefloquine + primaquine + immunoglobulin/yes | Recovery |
| 2009/[39]                  | Republic of Korea               | 27/F    | 21,000                    | Myocarditis         | Microscopy/PCR/6990/μL          | Yes                  | Chloroquine/no                          | Recovery |
| 2009/[40]                  | India                            | 1/M     | 20,000                    | Severe anemia, intracranial bleeding, seizures | Microscopy/RDT/NR            | No                   | Chloroquine + quinine dihydrochloride + primaquine/yes | Recovery |
| 2010/[41]                  | Republic of Korea               | 52/M    | 40,000                    | Retinal hemorrhage, jaundice, spleen infarction | Microscopy/91,88/μL         | No                   | Chloroquine + primaquine/no            | Recovery |
Table 1 continued

| Year of publication/reference | Location of malaria acquisition | Age/sex | Platelet count/μL (nadir) | Other complications | Diagnostic method/parasite density | P. falciparum excluded | Treatment/platelets transfusion (N unit) | Outcome |
|------------------------------|---------------------------------|---------|--------------------------|---------------------|-----------------------------------|-----------------------|------------------------------------------|---------|
| 2010/[42] Brazil             | 16/M                            | 12.000  | Rhabdomyolysis; renal failure | Microscopy/PCR/1520/μL | Yes | Chloroquine + artesunate + clindamycin/no | Recovery |
| 2010/[43] India              | 8/F                             | 21.000  | Petechial rash; severe anemia (Hb 4.7 g/dL); hematemesis | Microscopy/bone marrow/RDT/1.5 % | Yes | Chloroquine + primaquine/no | Recovery |
| 2010/[43] India              | 50/M                            | 19.000  | ARDS, hypotension | Microscopy/NR | No | Artesunate + primaquine/no | Recovery |
| 2010/[45] India              | 17/M                            | 34.000  | Acute pancreatitis; shock | Microscopy/RDT/NR | Yes | NR/No | Died |
| 2010/[46] Malaysia           | 38/M                            | 41.000  | ARDS | Microscopy/PCR/16/μL | Yes | Artesunate + primaquine/no | Recovery |
| 2010/[47] India              | 19/F                            | 45.000  | Acute myocarditis | Microscopy/RDT/NR | Yes | Artesunate + doxycycline/no | Recovery |
| 2010/[48] India              | 11/M                            | 27.000  | Petechial rash; jaundice; acute renal failure; GI bleeding, shock | Microscopy/RDT/NR | No | Artesunate/yes (NR) | Recovery |
| 2010/[49] Republic of Korea  | 59/M                            | 37.000  | ARDS; acute renal failure, jaundice; lactic acidosis | Microscopy/RDT/16,380/μL | Yes | Artesunate + chloroquine + primaquine/no | Recovery |
| 2010/[50] Greece             | 42/F                            | 24.000  | ARDS; jaundice | Microscopy/PCR//0.007 % | Yes | Mefloquine + quinine + doxycycline + primaquine/no | Recovery |
| 2010/[51] India              | 8/F                             | 11.000  | GCS 7; haemophagocytic syndrome; acute renal failure; hypotension | Microscopy/bone marrow/RDT/NR | Yes | Artesunate + sulphadoxine-pyrimethamine + primaquine/no | Recovery |

F female, M male, Hb haemoglobin, NR not reported, RDT rapid diagnostic tests, ARDS acute respiratory distress syndrome, PCR polymerase chain reaction, ITP idiopathic thrombocytopenic purpura, AST alanine aminotransferase, GCS Glasgow Coma Score, GI gastrointestinal
Table 2 Clinical studies using severe thrombocytopaenia as a criterion of severe malaria

| References | Type of study/country | No patients with severe \textit{P. vivax} malaria/\textit{P. falciparum} malaria (%) | Exclusion of other infectious diseases | No patients with severe thrombocytopaenia among those with severe malaria (%) | No patients with bleeding manifestation (tipology) | Death |
|------------|----------------------|-------------------------------------------|---------------------------------|---------------------------------|---------------------------------|--------|
| [13]       | Prospective (adults)/India | 40/456 (0.08) | Yes (RDT)/PCR/Yes | 5 (12.5) | 2 (Severe epistaxis requiring blood and platelet transfusions) | 2 due to ARDS (none with Thp) |
| [14]       | Prospective (pediatrics)/India | 24/35 (68.6) | No/No | 17 (70.8)\(^b\) | 2 (Epistaxis) | None |
| [52]       | Retrospective (adults and pediatrics)/India | 17/221 (7.7) | No/No | 13 | NR | 3 (Pregnant women with ARDS) |
| [53]       | Retrospective (adults)/India | 28/30 (93.3) | No/No | 28 (83.3) | None | 2:1 ARDS, 1 CM (none with Thp) |
| [54]       | Retrospective (pediatrics)/India | 23/108 (21.3) | Yes (RDT)/No | 9/23 (39.1) | 3 (Petechiae, purpura) | 1: GI bleeding, DIC, renal failure |
| [55]       | Retrospective (adults)/India | 43/121 (35.5) | Yes (RDT)/No | 43 | None | 3 due to ARDS (none with Thp) |
| [56]       | Prospective (pediatrics)/India | 60/380 (15.8) | Yes (RDT)/Yes | 51/60 (85) | 44 (Epistaxis), 19 (hematemesis) | None |
| [57]       | Retrospective (adults)/India | 107/213 (50.2) | Yes (RDT)/No | 17 (15.8) | None | None |
| [58]       | Retrospective (pediatrics)/India | 45/131 (21.1) | Yes (RDT)/No | 17 (13) | 12 (NR) | 4.2 ARDS/ARF, 1 CM, 1 DIC |
| [59]       | Retrospective (pediatrics)/India | 54/261 (20.7) | Yes (RDT)/Yes | 20 (8.7) | 10 (NR) | None |
| [60]       | Prospective (adults and pediatrics)/India | 200/900 (22.2) | Yes (RDT)/No | 24/200 (12) | 4 (Purpuric eruptions) | 40 |
| [61]       | Prospective (adults)/India | 22/198 (11.1) | Yes (RDT + PCR)/No | 7/140 (50)\(^d\) | 9 (NR) | 2 CM and ARDS (none with Thp) |
| [62]       | Prospective (pediatrics)/India | 38/61 (62.3) | Yes (RDT)/No | 18/38 (47.4) | NR | 5 (3 ARDS) |
| [63]       | Prospective (pediatrics)/Pakistan | 397/128 (30.5) | No/No | 15 (38.5) | NR | 1 with GCS <10, convulsion (without Thp) |
| [64]       | Retrospective (adults)/India | 111/296 (37.5) | Yes (RDT + PCR)/No | 58/111 (52.2) | 16 (GI, genitourinary or respiratory tracts) | 3:8 acute myocardial infarction |
| [65]       | Retrospective (adults and pediatrics)/India | 83/359 (23.1) | No/No | 13 (15.7) | 4 (NR) | None |
| [66]       | Prospective (pediatrics)/Sudan | 18/18 (100) | No/No | 4 (22.2) | 2 epistaxis | None |
| Total      |                       | 952/3916 (24.3) | 11/17 (64.7)/3/17 (17.6) | 359/952 (37.7) | 106/3506 (3)/106/310 (34.2) | 66/952 (69) |

\(^a\) By polymerase chain reaction (PCR) or rapid diagnostic tests (RDTs)

\(^b\) All patients with less than 150.000 per μL were considered

\(^c\) Only some patients underwent RDT analysis

\(^d\) In this study severe thrombocytopaenia was considered with value <80.000 per μL

\(^e\) Only discordant samples

\textit{RDT} rapid diagnostic test, \textit{PCR} polymerase chain reaction, \textit{NR} not reported, \textit{Thp} thrombocytopaenia, \textit{CM} cerebral malaria, \textit{ARDS} acute respiratory distress syndrome
However, in a recent study conducted in Brazil and India on 778 patients with documented *P. vivax* mono-infection, platelet counts showed a very poor discriminative performance to identify criteria of severe disease and the authors concluded that thrombocytopenia should not be used to identify patients with *P. vivax* complications [70].

The second issue that deserves to be addressed when considering disease severity regards mortality. In other words: did patients whose death was attributed to *P. vivax* malaria die of malaria or with malaria?

This issue has been addressed in one study only which was conducted in Brazil and reported the autopsy findings of 17 patients who died of *P. vivax* malaria [5]. The authors reported during the study period (1996–2010) a case-fatality rate (CFR) for *P. vivax* malaria of 0.011 % (19/170.286), but in only four of the seventeen patients who underwent autopsy death could be exclusively attributed to *P. vivax* malaria, resulting in a CFR of 0.002 % [5]. Of note, the CFR of *P. vivax* malaria was 16-fold lower than the one observed for *P. falciparum* malaria in the same period (0.032 %, 12/36.854) [5]. In another study conducted in Papua, Indonesia, between January 2004 and September 2009, a post hoc clinical death audit of cases of pure *P. vivax* malaria resulted in a CFR of 0.12 per 1000 infections [71]. Of note, of the six fatal cases for whom vivax malaria was considered the primary cause of death, four were young children of less than 2 years of age (two of whom were malnourished), and the other two were adults in whom sepsis was concomitantly documented.

Moreover, in a retrospective analysis of 12,769 cases of imported *P. vivax* malaria observed in the UK over 27 years (1987–2013), seven deaths were registered, giving an overall mortality of 0.05 %. The median age of deceased patients was 72 years, while no deaths occurred in the 9927 patients aged less than 50 years [72]. In the two studies regarding imported *P. vivax* malaria conducted by the TropNetEurope and the GeoSentinel network, reporting respectively 618 and 278 patients (either travellers or immigrants), no deaths were recorded among patients affected by this species of *Plasmodium* [73, 74].

Thus, based on available data, the mortality risk of *P. vivax* malaria seems to be different in endemic areas as opposed to what is observed in cases of imported disease in Europe or USA. In endemic areas, the risk of death is low and influenced by several factors, such as very young age, severe anaemia at presentation, malnutrition, pregnancy, coexisting comorbidities and concurrent infections [69–71, 75]. When imported *P. vivax* malaria is considered, the risk of death is generally absent or negligible and principally influenced by old age. Another important issue that should be considered when comparing malaria mortality is the lack of high level supportive care in many countries where malaria is endemic a factor that explains the better outcome observed in non-endemic countries where high-quality healthcare is available [76]. Despite these considerations it should be emphasized that the risk of death directly attributable to *P. vivax* malaria should not be overlooked.

In conclusion, given the lack of high quality studies and the fact that several confounding factors cannot be ruled out in the majority of case reports and studies published so far, the role of severe thrombocytopenia as an indicator of *P. vivax* malaria severity cannot at present neither be discarded nor confirmed and it deserves to be addressed in well conducted prospective studies in both endemic and non-endemic countries.

**Abbreviations**

ED: emergency department; WHO: World Health Organization; ICU: intensive care unit; G6PD: glucose-6-phosphate dehydrogenase; PCR: polymerase chain reaction; CFR: case-fatality rate; DIC: disseminated intravascular coagulation.

**Authors’ contributions**

All authors contributed to the content of this case report. SA performed the clinical assessments, data collection and drafted the manuscript. AC treated the patient in the ICU. AL R and LM searched the literature and drafted manuscript LG treated the patient until discharge and drafted the manuscript. MC performed the clinical assessments and drafted the manuscript. OR performed the molecular diagnostic and drafted the manuscript. All authors read and approved the final manuscript.

**Author details**

1 Department of Clinical and Biomedical Sciences Luigi Sacco, III Division of Infectious Diseases, University of Milano, Via GB Grassi, 74, 20157 Milan, Italy.

2 Intensive Care Unit Luigi Sacco Hospital, Milan, Italy.

**Consent for publication**

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

**Competing interests**

The authors declare that they have no competing interests.

**Received:** 17 September 2015  **Accepted:** 4 February 2016

**Published online:** 19 February 2016

**References**

1. Getting PW, Elyazar IRF, Moyes CM, Smith DL, Battle KE, Guerra CA, et al. A long neglected world malaria map. *Plasmodium vivax* endemicity in 2010. *PLoS Negl Trop Dis.* 2012;6:e1814.

2. Marchalavala E, Bignami A, Mannaberg J. Two monographs on malaria and the parasites of malarial fevers. London: New Sydenham Society; 1894.

3. Nulieia S, Syaffruddin D, Elyazar IRF, Baird J.K. Serious and fatal illness associated with falciparum and vivax malaria among patients admitted to hospital at West Sumba in eastern Indonesia. *Am J Trop Med Hyg.* 2012;87:41–9.

4. Alexandre MA, Ferreira CO, Siqueira AM, Magalhaes BL, Mourao MP, Lacerda MV, et al. Severe *Plasmodium vivax* malaria, Brazilian Amazon. *Emerg Infect Dis.* 2010;16:1611–4.

5. Lacerda MV, Fragoso SC, Alecrim MG, Alexandre MA, Magalhaes BM, Siqueira AM, et al. Postmortem characterization of patients with clinical diagnosis of *Plasmodium vivax* malaria: to what extent does this parasite kill? *Clin Infect Dis.* 2012;55:e67–74.
manifestations of *Plasmodium vivax* malaria in children: a retrospective study. J Clin Diagn Res. 2013;7:1964–7.

60. Sarkar D, Ray S, Saha M, Chakraborty A, Talukdar A. Clinicoscientific profile of severe *Plasmodium vivax* malaria in a tertiary care centre in Kolkata. Trop Parasitol. 2013;3:53–7.

61. Jain V, Agrawal A, Singh N. Malaria in a tertiary health care facility of Central India with special reference to severe vivax: implications for malaria control. Pathog Glob Health. 2013;107:299–304.

62. Singh R, Kumar S, Rana SK, Thakur B, Singh SP. A comparative study of clinical profiles of vivax and falciparum malaria in children at a tertiary care centre in Uttarakhand. J Clin Diagn Res. 2013;7:2234–7.

63. Shaik S, Memnon H, Shaik A, Ahmed L, Johano B, Baird KJ. Severe disease in children hospitalized with a diagnosis of *Plasmodium vivax* in southeast Pakistan. Malar J. 2012;11:144.

64. Zubairi AB, Nizami S, Raza A, Mehrjau AF, Rasheed AF, Ghanchi NK, et al. Severe *Plasmodium vivax* malaria in Pakistan. Emerg Infect Dis. 2013;19:1851–4.

65. Arboleda M, Perez MF, Fernandez D, Usuga LY, Mejia M. (Clinical and laboratory profile of *Plasmodium vivax* malaria patients hospitalized in Apartado, Colombia) (in Spanish). Biomedica. 2012;32 (Suppl):58–67.

66. Mahgoub H, Gasim GI, Musa IR, Adam I. Severe *Plasmodium vivax* malaria among sudanese children at New Halfa hospital, Eastern Sudan. Parasit Vectors. 2012;5:154.

67. Magalhaes BM, Siqueira AM, Souza MS, Gimaque JB, Bastos MS, et al. *P. vivax* malaria and dengue fever co-infection: a cross-sectional study in the Brazilian Amazon. PLoS Neglect Trop Dis. 2014;8:e3239.

68. Leal-Santos FA, Silva SB, Crepaldi NF, Nery AF, Martin TO, Alves-Junior ER, et al. Altered platelet indices as potential markers of severe and complicated malaria caused by *Plasmodium vivax*: a cross-sectional study. Malar J. 2013;12:462.

69. Lampah DA, Yeo TW, Malloy M, Kenangalem E, Douglas NM, Ronaldo D, et al. Severe malarial thrombocytopenia: a risk factor for mortality in Papua, Indonesia. J Infect Dis. 2015;211:623–34.

70. Siqueira AM, Lacerda MV, Magalhaes BM, Mourao MP, Melo GC, Alexandre MA, et al. Characterization of *Plasmodium vivax*-associated admissions to reference hospitals in Brazil and India. BMC Med. 2015;13:57.

71. Douglas NM, Ponscoro G, Lampah DA, Yeo TW, Kenangalem E, Poepoprindo JP, et al. Mortality attributable to *Plasmodium vivax* malaria: a clinical audit from Papua, Indonesia. BMC Med. 2014;12:217.

72. Broderick C, Nadjm B, Smith V, Blaze M, Checkley A, Childs PI, et al. Clinical, geographical, and temporal risk factors associated with presentation and outcome of vivax malaria imported into the United Kingdom over 27 years: observational study. BMJ. 2015;350:h1703.

73. Muhlbberger N, Jelinek T, Gascon J, Probst M, Zoller T, Schunk M, et al. Epidemiology and clinical features of vivax malaria imported to Europe: sentinel surveillance data from TropNetEurope. Malar J. 2004;3:5.

74. Leder K, Black J, O’Brien D, Greenwood Z, Kain KC, Schwartz E, et al. Malaria in travelers: a review of the GeoSentinel Surveillance Network. Clin Infect Dis. 2004;39:1104–12.

75. Saravu K, Rishikesh K, Kamath A, Shastry AB. Severity in *Plasmodium vivax* malaria claiming global vigilance and exploration- a tertiary care centre-based cohort study. Malar J. 2014;13:304.

76. Marks ME, Armstrong M, Suvan MM, Batson S, Whitty CJ, Chiodini PL, et al. Severe imported falciparum malaria among adults requiring intensive care: a retrospective study at the hospital for tropical diseases. London. BMC Infect Dis. 2013;13:118.