



TO THE EDITOR:

Access to emergency departments for acute events and identification of sickle cell disease in refugees

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Throughout the last decade, thousands of refugees arrived on a daily basis at the Mediterranean coast of Southern European countries. Because this influx is not expected to slow down, the development of national and European strategies is required to ensure appropriate and accessible health care to these vulnerable populations.^{1,2} The vast majority of these migrants come from areas in which sickle cell disease (SCD) and other hemoglobinopathies are highly prevalent. Limited data are available on the burden of these disorders in populations of refugees. Here, we present 2 pieces of evidence supporting the need for specific strategies for the early identification of SCD in refugees. First, we carried out a retrospective study of data collected from 2014 to 2017 across 13 Italian reference centers for SCD and hemoglobinopathies. The primary outcome of this study was to identify events associated with the new diagnosis of SCD in refugees; the secondary outcome was to evaluate the impact of hemoglobinopathies in refugees coming from endemic areas. The descriptive analysis of variables was performed with counts, percentages, mean and standard deviation (SD), or median and interquartile range (IQR; 25th-75th percentile). Then, we discuss the results of a pilot study that screened all refugees seen in a single second-level refugee center during October 2017, using 1 of the new rapid point-of-care screening devices (Sickle SCAN; BioMedomics). The aim was to fast-track the care of individuals with SCD and the collection of relevant demographic data.³⁻⁵ The results were validated by high-performance liquid chromatography, the standard gold-standard screening method.³⁻⁵

Based on data from the Italian Ministry of the Interior, a total of 624 688 refugees landed on the Italian coast between 2014 and 2017 (Figure 1A).⁶ Refugees from Syria represented only 4% to 25% of these each year (Figure 1A-B), whereas 21% to 53% came from sub-Saharan African countries (21% in 2014, 31% in 2015, 53% in 2016, and 46% in 2017). Refugees generally disembark at known hotspots on the coast of Southern Italy. They are then relocated in second-level reception centers throughout the country, before being screened for communicable diseases

and undergoing the vaccination program recommended by the World Health Organization within 2 weeks of their arrival. Screening for noncommunicable disorders, such as SCD, is not conducted. SCD is a common red cell disorder identified as a global health priority by the African Union and the World Health Organization.^{7,8} Life-threatening complications of SCD include acute vaso-occlusive painful events, acute chest syndrome, and splenic sequestration, which require early identification and intensive clinical management. In addition, dehydration, psychological stress, and exposure to high/low temperatures can trigger vaso-occlusive events in patients with SCD. Refugees represent marginalized and vulnerable people who are exposed to extreme conditions during their travels, mostly through Africa, to the coast of Southern European countries. The delay in the identification of SCD may lead to severe acute organ complications and fatal outcomes.^{9,10} To help manage acute health problems related to SCD that might dominate the first phase of transition of refugees, we have developed an algorithm for the management of acute events in the emergency department (ED) and we promoted specific knowledge of SCD, with training sessions and seminars dedicated to physicians in EDs, pediatricians, hematologists, and internal medicine physicians.¹⁰

Our retrospective study shows that SCD is relatively common in refugees visiting EDs for acute sickle cell–related events. Over the 4 years studied, we identified 70 patients with hemoglobinopathies: 50% were adults (86% male; 14% female; median age, 21 years; IQR, 18.5-19 years), and 50% were children (80% male; 20% female; median age, 10 years; IQR, 1-16 years). The number of refugees with SCD arriving in Italy between 2014 and 2017 revealed a peak in 2016 (48%) corresponding to the arrival of a large number of refugees from sub-Saharan Africa (41%) (Figure 1). The overall genotypic distribution was as follows: SS (n = 49), SC (n = 9), S β -thalassemia (n = 3), CC (n = 2), AS (n = 1), and transfusion-dependent β -thalassemia (TDT; n = 6). The analysis of genotypes combined with patient origin revealed that 61.4% of the SS individuals identified were from sub-Saharan

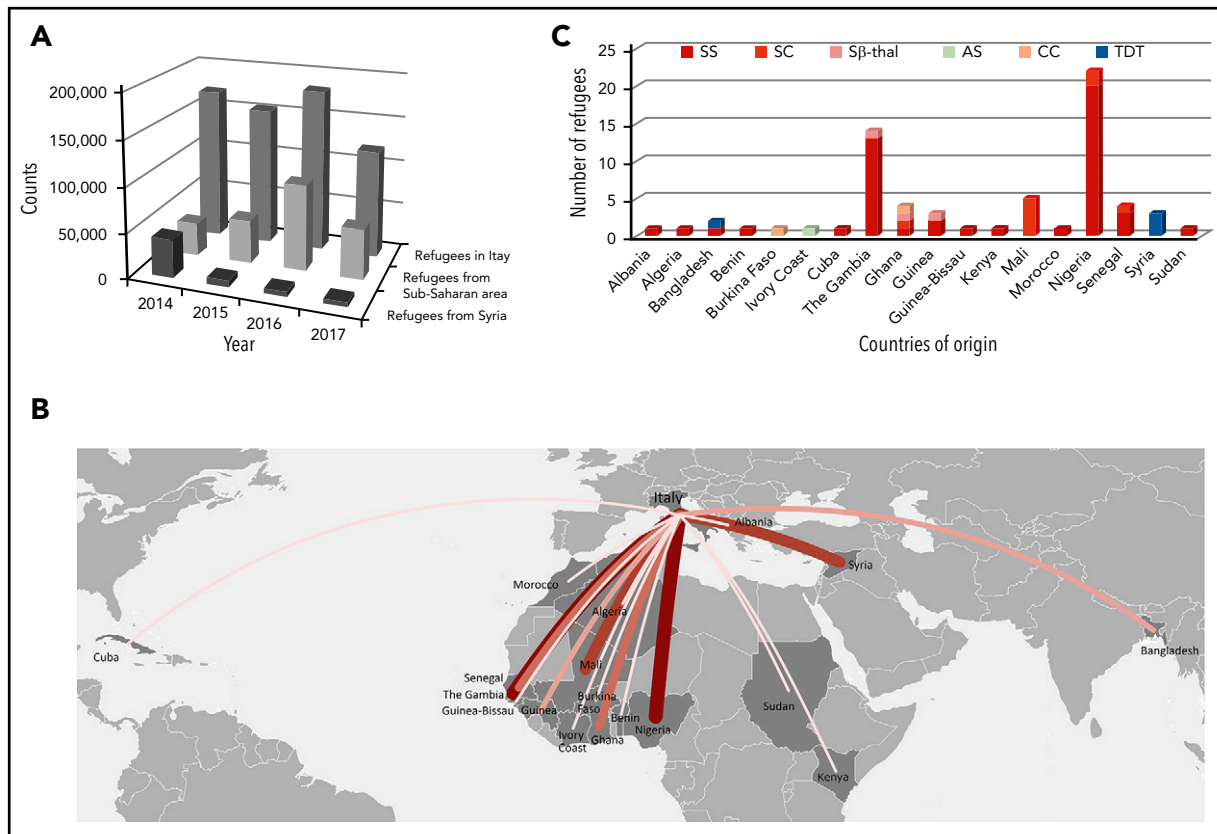


Figure 1. Numbers and country of origin of refugees in Italy with new identified severe hemoglobinopathy. (A) Numbers of total refugees in Italy, refugees from the sub-Saharan area, and refugees from Syria in the period between 2014 and 2017. (B) Map showing the influxes of refugees identified with hemoglobinopathies (SCD or TDT) after their arrival in Italy between 2014 and 2017. Countries of origin are shown in dark gray. The number of refugees from a country is proportional to the width and saturation of each line. (C) Numbers of patients with hemoglobinopathies (SCD or TDT) differentiated by genotype, as a function of nationality.

Africa (Figure 1C). SC patients were mainly from West African countries, whereas TDT patients were from Syria (7.1%) and Bangladesh (1.4%) (Figure 1C). As shown in Figure 2A, acute events were primarily responsible for the identification of SCD in refugees. The main reasons for access to ED of previously undiagnosed SCD were qualitatively similar to those seen in the native Italian SCD population¹¹ or other SCD groups,^{12,13} with the exception of anemia, which was the second main cause of visits to the ED in our study population. Although we did not have access to historical patient hematologic data, we cannot exclude the possible contribution of malnutrition to anemia in refugees with SCD. Among the individuals with SCD for whom hemoglobin (Hb) data were recorded ($n = 46$), 15% had Hb levels <8 g/dL, and 85% had Hb levels ≥ 8 g/dL. This is consistent with a recent report of data from German refugee centers, in which anemia was recognized in 22.5% of the refugees.¹⁴ A total of 82.9% of patients was diagnosed with SCD within the first 11 months after their arrival in Italy, and 14.3% were diagnosed during the second year. The main identifying signs of SCD in our group of patients are summarized in Figure 2A; in a small group, SCD was also identified outside acute events. Among these, 2.9% were identified through early pregnancy counseling or through the management of pregnancy complications related to severe clinical manifestations due to SCD (venous cerebral thrombosis, 1.4%) or obstetrical complications (spontaneous abortion, 1.4%).¹⁵ Collectively, our results indicate the need for screening for SCD in refugees at their

arrival to prevent severe acute and life-threatening clinical manifestations. This is also supported by a document from the Division of Global Migration and Quarantine of the US Department of Health and Human Services,¹⁶ as well as by the introduction of SCD screening by Canadian health authorities because of the increasing prevalence of SCD related to migration fluxes in North America.¹⁷ Indeed, our prospective study screening asymptomatic refugees in a second-level refugee center identified 3% SCD patients and 20% AS individuals over 400 screened individuals. The analysis of genotypes, combined with data on patients' origins, revealed that 2.6% of SCD patients were from sub-Saharan Africa. HbS carriers were from Nigeria (11.5%), Guinea (2.6%), Ivory Coast (2.1%), and Senegal (1.6%), whereas 0.5% each were from Burkina Faso, Gambia, Ghana, and Guinea Bissau; HbC carriers were from Ivory Coast (1%), Ghana (1%), Guinea (1%), Mali (0.5%) and Nigeria (0.5%); HbD carriers were from Nigeria (0.5%); and the β -thalassemia carriers were from Gambia (0.5%) and Guinea (0.5%). A total of 71.4% of the individuals screened did not have any hemoglobinopathy. None of the newly identified SCD patients were aware of their condition.

Because SCD and β -thalassemia are endemic to several parts of Italy, a national network of reference centers has been established in the last 5 decades for the clinical management of these patients, ensuring preconception counseling and prenatal diagnosis.¹⁸ In addition, this network allowed the identification of the ongoing epidemiological change across the country.^{11,19-21}

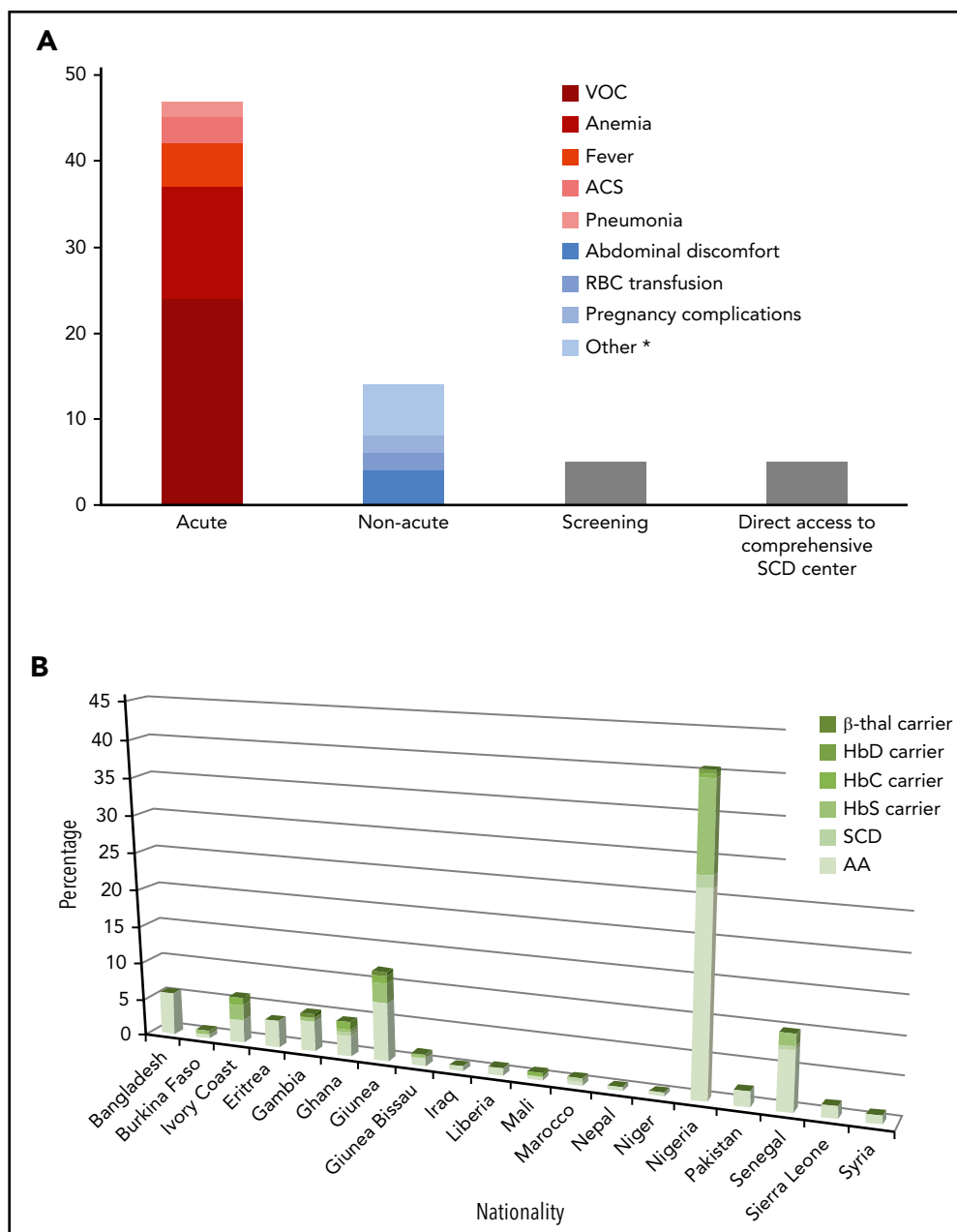


Figure 2. In refugees, the identification of new patients with severe hemoglobinopathy might result from the intersection of patients with acute events and screening programs for individuals from endemic areas. (A) Type and frequency of acute and nonacute events in refugees allowing the identification of a severe hemoglobinopathy in Italy between 2014 and 2017. *Other includes cardiopathy (n = 1), seizures (n = 1), splenic infarction and thrombosis of central retinal vein (n = 1), left gonalgia in severe gonarthrosis and joint deformities in septic arthritis outcomes (n = 1), inconsolable crying of a baby (n = 1), and genetic counseling for the second pregnancy of a mother (n = 1). (B) Percentages of patients screened, in a second-level refugee center with the new point-of-care screening device, as a way of fast-tracking the individuals with SCD, differentiated by genotype, as a function of nationality.

This makes the Italian experience unique compared with other European countries with a lower incidence of SCD. In our study, refugees with SCD were all redirected to the comprehensive SCD centers of the area. 60% of them were admitted or referred to an SCD center within 11 months after their first visit to an ED, and 32.9% within the second year. Patients with SCD were treated with hydroxyurea and followed-up by the comprehensive SCD centers of the area. A multidisciplinary working group on health care in refugees is now analyzing the possibility of introducing routine screening of SCD as a noncommunicable disorder in refugees.

In conclusion, our data support the recommendation that refugees coming from areas endemic for SCD should be screened for the disease. To appropriately address this problem and to face the dynamic changes in the distribution and prevalence of SCD in European countries, we propose (1) the development of flow charts facilitating the early and systematic identification of SCD in refugees at their arrival or in second-level refugee camps; (2) to educate health professionals, such as ED physicians, pediatricians, internal medicine doctors, and hematologists, about the early identification and treatment of acute vaso-occlusive events; (3) to rapidly refer refugees with SCD or symptomatic

HbS-carrier refugees to the comprehensive SCD reference center for treatment and follow-up; and (4) to rapidly start disease-modifying treatment, such as hydroxyurea. These actions will allow for the earlier identification of patients with SCD, preventing severe complications and decreasing the overall health care costs associated with this population.

Acknowledgments

BioMedomics provided Sickle SCAN devices as a restricted donation.

This work was supported by Fondo Universitario di Ricerca-Università degli Studi di Verona (L.D.F.) and by Società Italiana Talassemie ed Emoglobinopatie (B.G.).

Authorship

Contribution: L.D.F., F.B.P., and G.L.F. designed the study, analyzed the data, and wrote the manuscript; B.G. analyzed the data and wrote the manuscript; and C.L., F.B., M.C., G.G., R.L., V.P., M.C.P., P.R., R.R., G. Ruffo, G. Russo, V.S., C.P., M.R., and F.M. were involved in clinical identification of SCD and data collection.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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Footnote

There is a *Blood* Commentary on this article in this issue.

REFERENCES

1. Ledoux C, Pilot E, Diaz E, Krafft T. Migrants' access to healthcare services within the European Union: a content analysis of policy documents in Ireland, Portugal and Spain. *Global Health*. 2018;14(1):57.
2. Puchner K, Karamagioli E, Pikouli A, et al. Time to rethink refugee and migrant health in Europe: moving from emergency response to integrated and individualized health care provision for migrants and refugees. *Int J Environ Res Public Health*. 2018;15(6):E1100.
3. Nguyen-Khoa T, Mine L, Allaf B, et al. Sickle SCAN™ (BioMedomics) fulfills analytical conditions for neonatal screening of sickle cell disease. *Ann Biol Clin (Paris)*. 2018;76(4):416-420.
4. Segbena AY, Guindo A, Buono R, et al. Diagnostic accuracy in field conditions of the sickle SCAN® rapid test for sickle cell disease among children and adults in two West African settings: the DREPATEST study. *BMC Hematol*. 2018;18(1):26.

5. McGann PT, Hoppe C. The pressing need for point-of-care diagnostics for sickle cell disease: A review of current and future technologies. *Blood Cells Mol Dis*. 2017;67:104-113.
6. Italian Interior Ministry. Cruscotto statistico giornaliero. <http://www.libertacivilimmigrazione.dlci.interno.gov.it/it/documentazione/statistica/cruscotto-statistico-giornaliero>. Accessed 18 June 2018.
7. Modell B, Darlison M. Global epidemiology of haemoglobin disorders and derived service indicators. *Bull World Health Organ*. 2008;86(6):480-487.
8. Weatherall DJ, Clegg JB. Inherited haemoglobin disorders: an increasing global health problem. *Bull World Health Organ*. 2001;79(8):704-712.
9. De Franceschi L, Cappellini MD, Olivieri O. Thrombosis and sickle cell disease. *Semin Thromb Hemost*. 2011;37(3):226-236.
10. Forni GL, Finco G, Graziadei G, et al. Development of interactive algorithm for clinical management of acute events related to sickle cell disease in emergency department. *Orphanet J Rare Dis*. 2014;9(1):91.
11. Rigano P, De Franceschi L, Sainati L, et al; Italian Multicenter Study of Hydroxyurea in Sickle Cell Anemia Investigators. Real-life experience with hydroxyurea in sickle cell disease: A multicenter study in a cohort of patients with heterogeneous descent. *Blood Cells Mol Dis*. 2018;69:82-89.
12. Brousseau DC, Owens PL, Mosso AL, Panepinto JA, Steiner CA. Acute care utilization and rehospitalizations for sickle cell disease. *JAMA*. 2010;303(13):1288-1294.
13. Carroll CP, Haywood C Jr, Fagan P, Lanzkron S. The course and correlates of high hospital utilization in sickle cell disease: evidence from a large, urban Medicaid managed care organization. *Am J Hematol*. 2009;84(10):666-670.
14. Jablonka A, Wetzke M, Sogkas G, et al. Prevalence and types of anemia in a large refugee cohort in Western Europe in 2015. *J Immigr Minor Health*. 2018;20(6):1332-1338.
15. Vianello A, Vencato E, Cantini M, et al. Improvement of maternal and fetal outcomes in women with sickle cell disease treated with early prophylactic erythrocytapheresis. *Transfusion*. 2018;58(9):2192-2201.
16. Thornburg CD, Ware RE. Children with sickle cell disease migrating to the United States from sub-Saharan Africa. *Pediatr Blood Cancer*. 2018;65(6):e27000.
17. Corriveau-Bourque C, Bruce AA. The changing epidemiology of pediatric hemoglobinopathy patients in Northern Alberta, Canada. *J Pediatr Hematol Oncol*. 2015;37(8):595-599.
18. Cao A, Galanello R, Rosatelli MC. Prenatal diagnosis and screening of the haemoglobinopathies. *Baillieres Clin Haematol*. 1998;11(1):215-238.
19. Colombatti R, Dalla Pozza LV, Mazzucato M, Sainati L, Pierobon M, Facchin P. Hospitalization of children with sickle cell disease in a region with increasing immigration rates. *Haematologica*. 2008;93(3):463-464.
20. Venturelli D, Lodi M, Palazzi G, et al. Sickle cell disease in areas of immigration of high-risk populations: a low cost and reproducible method of screening in northern Italy. *Blood Transfus*. 2014;12(3):346-351.
21. Lodi M, Bigi E, Palazzi G, et al. Universal screening program in pregnant women and newborns at-risk for sickle cell disease: first report from Northern Italy. *Hemoglobin*. 2017;41(4-6):230-233.

DOI 10.1182/blood-2018-09-876508

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