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ACCESS TO EMERGENCY DEPARTMENT FOR ACUTE EVENTS AND IDENTIFICATION OF SICKLE CELL DISEASE IN REFUGEES

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To the Editor:

Throughout the last decade, thousands of refugees arrived on a daily basis on the Mediterranean coast of Southern-European countries. As this influx is not expected to slow down, developing 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 two 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 during the period 2014-2017 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 and 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: 25^{th} - 75^{th} percentile). Then, we discuss the results of a pilot study which screened all refugees seen in a single second-level refugee center during October 2017, using one of the new rapid point of care screening devices (SickleSCAN® *BioMedomics, inc*.). The aim was to fast-track the care of individuals with SCD and the collection of relevant demographic data.[3-5] The results were then validated by HPLC, the standard gold-standard screening method.[3-5]

Based on data from the Italian Ministry of Interior, a total of 624,688 refugees landed on the Italian coast between 2014 and 2017 (Fig. 1A).[6] Refugees from Syria only represented 4-25% of these each year (Fig. 1A, B), while 21-53% came from sub-Saharan African countries (21% in 2014, 31% in 2015, 53% in 2016 and 46% in 2017). Refugees generally disembark on 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 (WHO) within two weeks after their arrival. Screening for non-communicable disorders (NCD) such as SCD is not conducted. SCD is a common red cell disorder identified as a global health priority by the African-Union and WHO.[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, psychologic stress, and exposure to high/low temperature can trigger vaso-occlusive events in patients with SCD. Refugees represent marginalized and vulnerable people, 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 managing acute health problems related to SCD which might dominate the first phase of transition of refugees, we have developed an algorithm for the management of acute events in emergency department (ED) and we promoted specific knowledge of SCD, with training sessions and seminars dedicated to physicians of the EDs, pediatricians, hematologists and internal medicine physicians.[10]

Our retrospective study shows that SCD is relatively common in refugees accessing ED for acute sickle cell related events. Over the four years studied, we identified 70 patients with hemoglobinopathies, with 50% of adults (86% male, 14% female, median age 21 years, IQR 18.5-19 years) and 50% of children (80% male, 20% female, median age 10 years, IQR 1-16 years). The counts of refugees and patients with SCD as a function of their origin revealed a peak of SCD identification in 2016 (respectively 17%, 17%, 48% and 17%), corresponding to the arrival of a large number of refugees from Sub-Saharan Africa (respectively 15%, 20%, 41%, 24%) (Fig. 1B).The overall genotypic distribution was as follow: SS (*n*=49), SC (*n*=9), Sβ-thalassemia (Sβ, *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 Africa (Fig. 1C). SC patients were mainly from West African countries, whereas, TDT patients were from Syria (7.1 %) and Bangladesh (1.4 %) (Fig. 1C). As shown in Fig. 2A, acute events were mainly 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 population[11] or other SCD groups, [12,13] except for anemia, which appeared to be the second main cause of access to 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. Amongst the individuals with SCD for which hemoglobin (Hb) data were recorded (*n*=46), 13% had Hb levels were <8 g/dL and 83% Hb levels were $\geq$ 8 g/dL. Although we have not access to historical patient hematologic data, we cannot exclude the possible contribution of malnutrition to anemia in refugees with SCD. This is consistent with a recent report of data from German refugee centers, where anemia was recognized in 22.5% of the

refugees.[14] 82.9% of patients were diagnosed with SCD within the first 11 months after their arrival in Italy, and 14.3 % during the second year. In a small group of refugees (*n*=14), SCD was also identified outside acute events and the main causes are summarized in Fig. 2A. Among these, 2.9 % were identified through early pregnancy counseling or through the management of complications in pregnancy related to (i) severe clinical manifestations due to SCD (venous cerebral thrombosis 1.4%); or (ii) obstetrical complications (spontaneous abortion, 1.4%).[15] Collectively, our results indicate the need of screening for SCD in refugees at their arrival in order 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 United State Department of Health and Human Service (2016)[16] and by the introduction of SCD screening by Canadian health authorities, due to the increasing prevalence of SCD related to migration fluxes in North America.[17] Indeed, data on our prospective study that screened all asymptomatic refugees in one 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%), Senegal (1.6%) and the 0.5% from Burkina Faso, Gambia, Ghana and Guinea Bissau respectively; 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%). 71.4% of the individuals screened did not have any hemoglobinopathy. None of the newly identified SCD patients was aware of their condition.

Since SCD and β-thalassemia are endemic in several parts of Italy, a national network of refence centers has been established in the last five decades for the clinical management of these patients, ensuring pre-conception counseling and pre-natal diagnosis.[18] In addition, this network allowed to identify the ongoing epidemiological change across the country.[11,19-21] This makes the Italian experience unique compared to other European countries with a lower incidence of SCD. In our study, refugees with SCD were all re-directed to the comprehensive SCD centers of the area. 60% of them were taken in charge within the first 11 months from their first access to an ED and 32.9 % within the second year. Patients with SCD were then placed under hydroxyurea treatment 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 NCD in refugees.

In conclusion**,** our data support the recommendation that SCD should be screened in refugees coming from endemic areas for SCD. To appropriately address this problem and to face the current situation of dynamic changes in the distribution and prevalence of SCD in European countries, we propose (i) to develop flow-charts facilitating the early and systematic identification of SCD in refugees at their arrival or in second level refugee camps; (ii) to educate health professionals such as ED physicians, pediatricians, internal medicine doctors and hematologists in the early identification and treatment of acute vaso-occlusive events; (iii) to rapidly refer SCD or symptomatic HbS-carrier refugees to the comprehensive-SCD-reference center for treatment and follow-up and (iv) to rapidly start disease modifying treatment such as HU. These actions will allow for an earlier identification of patients with SCD, preventing severe complications and decreasing the overall healthcare costs associated with this population.

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AUTHORSHIP AND CONTRIBUTIONS

LDF, PBP, GLF designed the study, analyzed the data and wrote the paper, BG analyzed the data and wrote the paper, CL, FB, MC, GG, RL, VP, MCP, PR, RR, GR, GRus, VS, CP, MR, FM were involved in clinical identification of SCD and data collection.

CONFLICT OF INTEREST AND DISCLOSURE

The authors have nothing to disclose. Biomedomics provided SickleSCAN® devices as a restricted donation.

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FIGURE LEGENDS

Fig 1. (A) Counts of total refugees in Italy, of refugees from Sub-Saharan area and from Syria in the period between 2014 and 2017. **(B)** Map showing the fluxes of refugees identified with hemoglobinopathies (sickle cell disease or transfusion dependent thalassemia-TDT) after their arrival in Italy between 2014 and 2017. Countries of origin are

shown in dark grey. The country of destination, Italy, is shown in dark red**. (C)** Counts of patients with hemoglobinopathies (sickle cell disease or transfusion dependent thalassemia-TDT), differentiated by genotype, as a function of the nationality.

Fig 2. (A) Type and frequency of acute and non-acute events identified in refugees identified with a hemoglobinopathies in Italy between 2014 and 2017. * Other include: 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 counselling for the second pregnancy of a mother (*n*=1). **(B)** Percentage 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 the nationality.

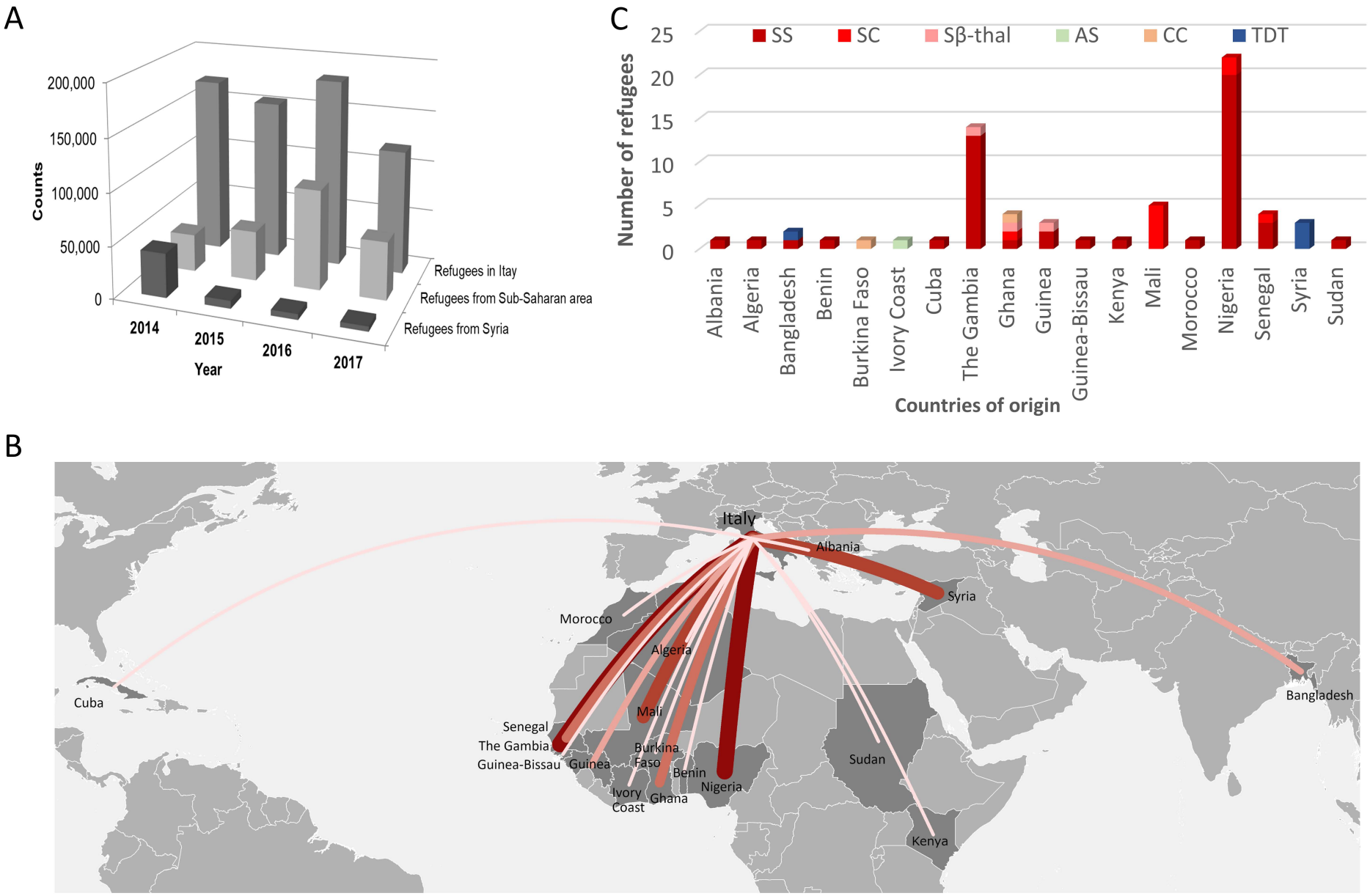
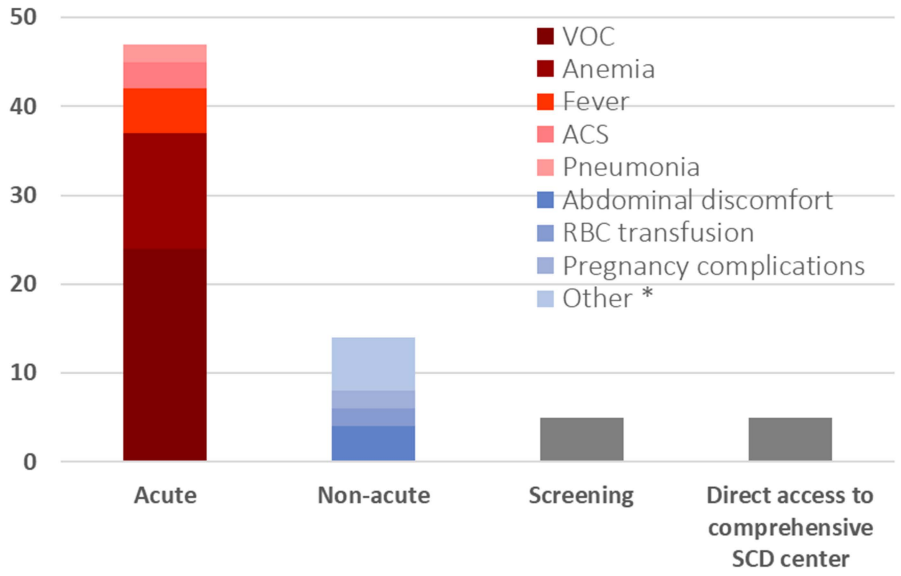

A
200,000
150,000
100,000
50,000
0
Counts
2014
2015
2016
2017
Year
Refugees in Itay
Refugees from Sub-Saharan area
Refugees from Syria
C
SS
SC
Sβ-thal
AS
CC
TDT
25
20
15
10
5
0
Number of refugees
Albania
Algeria
Bangladesh
Benin
Burkina Faso
Ivory Coast
Cuba
The Gambia
Ghana
Guinea
Guinea-Bissau
Kenya
Mali
Morocco
Nigeria
Senegal
Syria
Sudan
Countries of origin
B
Italy
Albania
Syria
Morocco
Algeria
Cuba
Mali
Senegal
The Gambia
Guinea-Bissau
Guinea
Burkina Faso
Benin
Nigeria
Ivory Coast
Ghana
Sudan
Kenya
Bangladesh

Figure 1

A


50
40
30
20
10
0
VOC
Anemia
Fever
ACS
Pneumonia
Abdominal discomfort
RBC transfusion
Pregnancy complications
Other *
Acute
Non-acute
Screening
Direct access to comprehensive SCD center

B

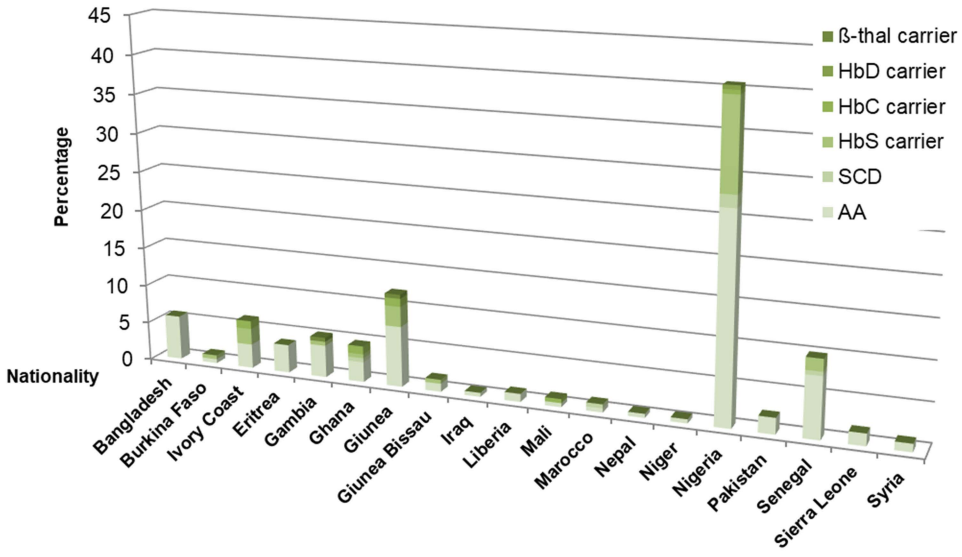

45
40
35
30
25
20
15
10
5
0
Percentage
Nationality
ß-thal carrier
HbD carrier
HbC carrier
HbS carrier
SCD
AA
Bangladesh
Burkina Faso
Ivory Coast
Eritrea
Gambia
Ghana
Giunea
Giunea Bissau
Iraq
Liberia
Mali
Marocco
Nepal
Niger
Nigeria
Pakistan
Senegal
Sierra Leone
Syria

Figure 2

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

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