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Survey of sickle cell disease in Italy

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ABSTRACT

Background and Objective. **The present study was designed to determine the distribution and severity of sickle cell disease (SCD) in Italy.**

Design and Methods. **A questionnaire, requesting information about the cases of sickle cell disease that had been seen during previous years, was sent to all Italian centers of Pediatrics and Hematology. The questionnaire was simple and required personal, hematologic and clinical information.**

Results. **A total of 696 cases were reported. The distribution of registered patients shows that, although the S gene originated mostly in Sicily and Southern Italy, 20% of patients with SCD now live in Central and Northern Italy. The types of SCD reported were as follows: compound heterozygotes HbS-β thalassemia, (S-Th, 518 cases); homozygotes for HbS, (S-S, 149 cases); compound heterozygotes HbS and another abnormal hemoglobin (21 cases). The population of patients with SCD is younger than the general Italian population. More than 90% of patients have had no crises or only a limited number, namely, up to 6/year. Infections ranged between 0 and 6/year. Splenomegaly was reported in 28% and 80% of adult patients with S-S and S-Th, respectively. The prevalence of gallstones was 48%.**

Interpretation and Conclusions. **The survey established that 1) sickle cell disease is widely distributed in Italy; 2) while the clinical spectrum is extremely variable, severe forms are infrequent.**

Key words: Caucasian, Italy, sickle cell disease, sickle cell anemia, survey

Sickle cell disease (SCD) is the most common genetic abnormality that afflicts people of African ancestry and it is the most frequent hemoglobinopathy in Italy. It is defined as a clinical abnormality due to the presence of only HbS (S-S) within the red cells, of HbS and another abnormal hemoglobin (S-other Hb), or of HbS with β-thalassemia (S-Th).

The disease is widespread in Africa and is also present in the Middle East, India, and in Southern European countries, as well as in people of African ancestry who live in North, Central and South America. Little is known about the distribution of SCD in people of European extraction[1] and previous reports on the prevalence of the disease in European countries have dealt with people of Indian and African ancestry.[2]

HbS is endemic in Sicily and this anomaly has been described in Sicilians and in people of Sicilian ancestry.[3] The consensus is that the gene was introduced into Sicily and Southern Italy from Northern Africa through the trans-Saharian trade routes, or, alternatively, by means of the Greek colonization, although the introduction of the gene into Sicily during the Muslim invasion cannot be excluded.[4] As a result of the domestic migration from Sicily and Southern Italy towards Northern Italy, the disease has spread over all of Italy. Moreover, recent immigration from foreign countries, in particular from Africa, has contributed to the further diffusion of the disease in Italy (Figure 1).

The aim of the present study was to determine the distribution S-S and S-Th in Italy in terms of: 1) the number of patients with the disease, 2) the location of these patients, and 3) the clinical severity of both S-S and S-Th diseases in Italian patients.

Materials and Methods

Collection of data

A questionnaire was sent to all Italian centers that participate in the "Cooley Care Program" and to other Divisions of Pediatrics and Hematology (132 centers). The questionnaire requested information about the cases of sickle cell disease that had been seen during previous years. It was divided into three sections. The first section included questions about the identification and the age of patients, the date of diagnosis, the town of parents' origin and the kinds of anomaly of which the parents were carriers (Hb S, β-thalassemia, Hb C or other abnormal hemoglobin), the town of residence, school attendance and employment conditions. In addition, information about numbers of pregnancies, abortions and deliveries was collected for adult females patients. Section 2 included requests for hematologic data at diagnosis or at least 6 months after the last transfusion (not presented in this report). Section 3 included requests for information about the clinical condition of

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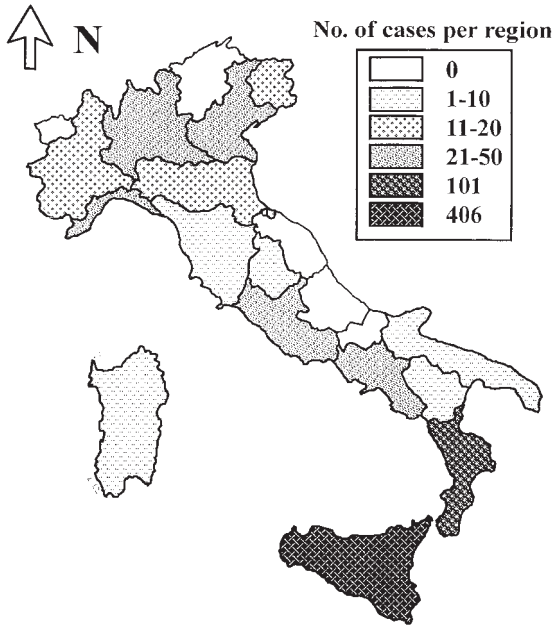

Figure 1. A map of Italy showing the prevalence of SCD reported in the various regions.

patients, namely the number of painful crises per year; the number and type of infections per year; the presence of the spleen and its enlargement; the age at splenectomy, if performed; the presence of gallstones and the age at cholecystectomy, if performed.

Analysis of data

Collected data were checked and entered on a Microsoft Excel worksheet on a personal computer. Statistical analyses were performed with the EpiInfo software, v.6.02 (CDC, Atlanta GA, USA). Comparisons with the general Italian population were made using data provided by ISTAT.[5,6]

Results

Replies were received from 79 of the 132 centers. Twenty-five of the 79 centers from which replies were received had no cases to report and, therefore, all the cases identified in the present survey were derived from 54 centers all over Italy. A total of 696 cases were reported. Eighty patients were reported by two or more centers and were assigned to the center that was able to give the most detailed information or to the one that was following the patient at the time of the survey.

Residence

The place of residence was unknown in 22 cases. One patient usually lived in Hannover (Germany) and came occasionally to Italy. The remaining 673 were distributed as follows: 406 (60.3%) in Sicily, 134 (19.9 %) in Southern Italy, 43 (6.3%) in Central Italy, and 90 (13.3%) in Northern Italy.

Origin of the S gene

The place of origin of the Hb S-carrier parents was given for 427 Italian parents. Most of them were born in Sicily (290, 67.9%), whereas 131 (30.7%) originated from Southern Italy, 3 (0.7%) from Central Italy and 3 (0.7%) from Northern Italy. Forty-four patients had non-Italian parents. Forty-two patients had two foreign parents. The country of origin was given for 38 couples, as follows: Angola, 3; Brazil, 3; Cape Verde Islands, 1; Central Africa, 1; Ghana, 15; Mauritius, 1; Nigeria, 10; Santo Domingo, 2; Togo, 1; Tunisia, 1; and Zaire, 1. Two patients had only one foreign parent from outside Italy, with a parent from Nigeria and the USA, respectively.

Type of SCD and sex

The reported diagnoses for the patients are listed in Table 1. Within the S-Th group it was possible to classify 138 patients as S-β^0Th and 34 patients as S-β^+Th. The type of β-thalassemia mutation was known in 125 patients: CD39 (46) IVS-I-110 (32), IVS-I-6 (20), IVS-I-1 (12), IVS-II-745 (9), IVS-II-1 (4), -87 (2). The sex distribution revealed no significant differences, except in the case of a higher prevalence of females among patients with S-S (Table 1).

Age

The date of birth of 33 patients was unknown. Table 2 shows the age distribution of the remaining 663 patients together with that of the general Italian population.

Age at diagnosis

This was unknown for 136 patients. Four patients were born after prenatal diagnosis had been performed. The remaining 556 patients were distributed as follows: 0-3 years, 290 patients (52.2%); 4-15 years, 183 patients (32.9%); and ≥16 years, 83 patients (14.9%); with no difference between patients with S-S and S-Th.

Table 1. Types of sickle cell disease and sex distribution.

Diagnosis	*Males*	*Females*	*No. of patients*	*%*
S-C	8	2	10	1.4
S-D Los Angeles	1	4	5	0.7
S-Lepore	2	2	4	0.6
S-δβTh	1	1	2	0.3
S-S	63	86*	149	21.4
S-Th	258	260	518	74.4
n.n.	6	2	8	1.1

**p=0.008 (χ^2=7.1) males vs. females.*

Table 2. Distribution of 663 patients with SCD and the Italian population by age.

Age class	*No. of patients*	*%*	*% Italian population*
0-9 years	116	17.5	9.9
10-19 years	172	25.9	14.4
20-29 years	161	24.3	15.4
30-39 years	138	20.8	13.9
40-49 years	39	5.9	12.8
50-59 years	25	3.8	12.3
60-69 years	9	1.4	10.1
≥70 years	3	0.5	11.3

p = 0.000001 (χ^2=331.7, goodness of fit).

Table 3. Number of crises per year for patients with S-S and S-Th.

*Pain rate**	*All pts (557)*	*S-S pts (123)*	*S-Th pts (419)*	*S-β^0th pts (138)*	*S-β^+th pts (34)*
r = 0	150 (27%)	24 (19.5%)	120 (28.6%)	37 (26.8%)	17 (50.0%)
0<r≤6	369 (66.3%)	84 (68.3%)	276 (65.9%)	72 (52.2%)	15 (44.1%)
7<r≤12	34 (5.9%)	14 (11.4%)	20 (4.8%)	4 (2.9%)	0 (0%)
r>12	4 (0.8%)	1 (0.8%)	3 (0.7%)	25 (18.1%)	2 (7.4%)

**r denotes the number of episodes of pain per patient-year; S-S vs. S-Th χ^2=9.7 p<0.05; S-b0th vs. S-b+th χ^2=8.61 p<0.05.*

Educational level achieved

Patients of 6 or more years of age, whose attendance at school was considered (383) were divided into categories, according to the educational level achieved (percentages for the general Italian population are given in parentheses): illiterate, 5, 1.3% (3.1%); literate with no schooling, 55, 14.4% (18.2%); primary school, 91, 23.8% (40.6%); junior secondary school, 122, 31.8% (23.8%); senior secondary school, 102, 26.6% (11.5%); and college or university, 8, 2.1% (2.8%); there was no difference between patients with S-S and S-Th.

Employment

Occupational status was known for 459 patients. A total of 178 were at an age where they were not employable, namely <14 or ≥70 years of age. The remaining 278 patients of working age were distributed as follows (percentages for the general Italian population are given in parentheses): non-workers, 126, 45.3% (31.9%); employed workers, 96, 34.6% (61.7%); and unemployed workers, 56, 20.1% (6.4%). Since there are wide variations in unemployment rates among different regions of Italy, an intra-regional comparison was also made: the rate of unemployment of patients living in Sicily was 21.2%, as opposed to 19.9% for the corresponding general population; there was no difference between patients with S-S and S-Th.

Pregnancy

Female patients over 18 years of age were considered (237). For 63 of them information about pregnancies was unavailable. Seventy-four had had no pregnancies and 100 had had one or more pregnancies, with a total of 179 pregnancies. Of the pregnancies, 149 ended in deliveries, 28 (15.6%, confidence limits 11-22%) ended in spontaneous abortion and 2 (1.1%) ended in voluntary abortion; there was no difference between patients with S-S and S-Th.

Painful crises

Painful crisis is defined as an acute episode of bone and/or abdominal pain leading to the use of analgesics with or without hospitalization. Numbers of crises per year are known for 557 patients, ranging between 0 and 24, with a median of 2 per year. The distribution of patients according to the number of crises and the type of SCD is given in Table 3. Patients with S-Th had fewer crises per year than those with S-S. Among the patients with S-Th, those with S-β^+th had a lower number of crises per year than those with S-β^0th (Table 3).

Bacterial infections

Numbers of episodes of infection during the previous year were reported for 557 patients. Numbers range between 0 and 6 (mean 0.4, median 0), for a total of 247 episodes. There was no difference between patients with S-S and S-Th (data not shown). A total of 223 episodes (90.3%) was reported as pneumonia (likely to be referred to as *acute chest syndrome*, see below in Discussion), 7 (2.8%) as osteomyelitis, 4 (1.7%) as cholecystitis, 2 (0.8%) as pericarditis, 2 (0.8%) as urinary tract infection, 2 (0.8%) as septicemia, and 7 (2.8%) as others.

Spleen

Information about spleen status was available for 554 patients, of whom 194 (35%) had been splenectomized. Among 124 patients with S-S, 25 (20%) had undergone splenectomy while, among 413 patients with S-Th, 167 (40.4%) had undergone splenectomy; there was a statistically significant difference between the two groups (χ^2=17.07, p<0.0001).

Of the remaining 360 unsplenectomized patients, 191 were aged 18 years or more. Among them, 121 (63.3%) had an enlarged spleen. Splenomegaly was present in a higher percentage of patients with S-Th aged 18 years or more (102/128 patients, 79.9%) than in patients with S-S (16/57 patients, 28.1%), and the difference was statistically significant (χ^2=49.09, p<0.0001). Patients with an enlarged

Table 4. Prevalence of gallstones in patients according to age.

Age (years)	*No. of patients*	*No. with gallstones*	*Prevalence of gallstones (%)*
5-9	66	8	12.1
10-19	151	49	32.5
20-29	143	69	48.3
≥30	167	125	74.8

spleen are younger than those with an unpalpable spleen (median age 18.5 vs. 21.6 years), but the difference was statistically significant only within the group of patients with S-S (Kruskal-Wallis test, H = 10.4, p<0.001).

Gallstones

There was no information about the presence of gallstones in 169 patients. In the 527 reported cases, the prevalence of gallstones, detected by means of ultrasonography, was 47.6%, with increases with age (Table 4). Gallstones were more prevalent in patients with S-S than in those with S-Th, and the difference was statistically significant (Table 5). Among patients with gallstones, those with S-S were significantly younger than those with S-Th. Cholecystectomy was performed, at a mean age of 22.7±8.7 years, in a higher percentage of patients with S-Th than in those with S-S (Table 5).

Discussion

The present survey established that sickle cell disease is widely distributed in Italy, but high concentrations of patients were found only in Sicily and Southern Italy. All Pediatric and Hematology Divisions, along with internal medicine units that are usually in charge of thalassemia patients, were asked to report their cases, and many responded. The 53 centers that did not reply were mainly small centers located in peripheral hospitals in Central and Northern Italy, which presumably had no cases to report since SCD originally spread from Sicily and Southern Italy toward Central and Northern Italy during the domestic migrations of people looking for better employment opportunities in the years after World War II. As a result, patients with SCD, as well as all people of Sicilian and Southern-Italian origin who moved to Northern Italy, live in large industrialized areas of Northern Italy. It is, therefore, reasonable to assume that small centers located in peripheral provinces had no cases to report. Nevertheless, the number of cases was certainly underestimated in this study because the subjects were recruited through hospitals and not through population-based surveys. In fact, the clinical spectrum of SCD in Sicily is extremely varied, ranging from severe forms to nearly asymptomatic forms.[7-10] The latter cases are usually diagnosed as SCD only when another member of the family suffers from a more severe form of the disease, sometimes at a rather advanced age. Such cases, when isolated in a family, might never need specific medical attention and, therefore, might be never diagnosed. Moreover, the distribution of SCD in Italy is changing because of the recent immigration from extra-European countries, and from Africa in particular. The cases of patients of foreign ancestry that were registered in the present survey are those of patients who have immigrated legally. Presumably, there are other individuals with SCD living illegally in Italy, who never seek medical assistance.

The analysis of the place of origin of carriers of Hb S showed that the S gene originated mostly in Sicily and Southern Italy, with only a few (1.4%) S-carrier parents originating from Central and Northern Italy. By contrast, the distribution of patients indicated that 20% of SCD patients now live in Central and Northern Italy, and mainly in the industrialized areas of Northern Italy. This observation underscores the need for every Italian physician to be aware of the fact that SCD is no longer a region-restricted health problem, and for Pediatric and Hematology centers to consider the needs of patients with SCD. Mass screening campaigns for the identification of heterozygous carriers of a hemoglobin anomaly should be undertaken all over Italy. They should include the search for HbS (by means of hemoglobin electrophoresis or HPLC) and not rely only on microcytosis, which is a basic feature of β-thalassemia but not of HbS heterozygous carriers.

Table 5. Gallstones in 527 patients.

	All (527)		*S-S (123)*		*S-Th (389)*	
	N.	*%*	*N.*	*%*	*N.*	*%*
Patients with gallstones	251	47.6	71	57.7	177	45.5*
Patients with gallstones who underwent cholecystectomy	94	64.4	25	50	69	72.6°
Mean age of patients with gallstones ± SD (range)	29.1±12.5 (5-72)		26.1 ± 12.8 (5-59)		30.4 ± 12.2 (9-72)#	

**S-S vs. S-Th χ^2 p<0.05; °S-S vs. S-Th χ^2 p<0.01; #S-S vs. S-Th t –3.36 p<0.0001.*

Furthermore, physicians all over the world should be aware of the possibility that SCD can afflict so-called Caucasian people[1] and consider the results of the Italian survey as an example of how past and recent migrations are changing the geographic diffusion of genetic diseases. Such a phenomenon could well occur anywhere in the world for any inherited disorder.

The age distribution of the patients with SCD clearly showed that the patient population was younger than the general Italian population. Nonetheless, half of the patients (56.7%) were adults and some of them had reached old age: 5.7% were above 50 years of age and 3 patients were more than 70 years of age. Perhaps better management has allowed more children to survive to adulthood. Furthermore, there are many patients whose clinical manifestations of the disease are so mild that they easily survive until adulthood. Thus, even though most patients were diagnosed as having SCD early in life (52.2% before 3 years, and 85.1% before 15 years), approximately 15% were diagnosed in adulthood.

Analysis of the educational level of the patients in comparison with the general Italian population revealed a lower prevalence of illiterates, of literates with no education, and of individuals with a primary-school education, and a higher prevalence of individuals with junior-secondary school and senior-secondary school education. These differences might be due to the different age distribution of patients as compared to the general population, the latter being older. It is well known that a lower level of education is more frequent among older individuals. In any case, our data indicate that school attendance by patients with SCD is satisfactory.

The unemployment rate was higher than the general Italian rate. However, since there are wide variations in unemployment rates among the different regions of Italy, we compared the unemployment rate of patients living in Sicily with the Sicilian regional rate of unemployment and we found no difference. Thus, patients with SCD have the same chance as other individuals of getting a job.

The rate of spontaneous abortion in our cohort of patients was only slightly higher than the rate reported for the general population, which ranges from 8 to 15%,[11] reflecting the reported decrease in the rate of spontaneous abortions for patients with SCD during the last three decades.[12]

Pain, which is a major feature of SCD,[13] was also evaluated. Numbers of painful crises ranged from 0 and 24 with a mean of 2/year. More than 90% of patients had no crises or only a limited number, namely up to 6 per year. The patients with S-Th and, among them, patients with S-β^+Th experienced fewer crises per year. The wide distribution confirms the extreme variability of the clinical spectrum of SCD in Italy, as reported previously.[3,7-10]

The infection most commonly reported was pneumonia, as also reported previously in Sicilian patients.[8] However, since it is difficult, and in some instances impossible, to distinguish between pneumonia and lung infarction in the absence of a positive culture test, we cannot exclude the possibility that such episodes did not always involve an infectious agent and, therefore, it seems more appropriate to refer to them as episodes of acute chest syndrome, whose frequency has been reported to be 15 to 43%.[14-16] By contrast, the incidence of other infectious diseases, such as septicemia, meningitis and osteomyelitis, which have been reported to be frequent in other series,[17] were infrequent in our patient population. In particular only two episodes of septicaemia and no cases of meningitis were reported for 557 patients, while seven episodes of osteomyelitis were reported, namely 0.01 episodes per patient/year. The low frequency of infectious diseases, apart from episodes of acute chest syndrome, might have several explanations: 1) Caucasian patients suffer from a mild form of the disease; 2) the extensive use of prophylactic penicillin is able to prevent infections; 3) the endemic nature of most infectious diseases in Italy might account for subclinical infections and contacts with pathogens might result in active immunization early in life. No differences were detected among the different genotypes with respect to the number or type of infections.

During the natural course of SCD, the spleen increases in size and becomes palpable during the first months of life. However, recurrent episodes of vaso-occlusion and infarction cause a decrease in splenomegaly over the years. Splenomegaly was found in 19% of Greek patients with S-S and only in 5% of Jamaican patients with S-S who were over 18 years of age,[18] while it was present in 28% of Italian patients with S-S. The greater persistence of splenomegaly in the Italian patients can be explained by the lower degree of tissue infarction in Italian patients, since hypersplenism can be excluded on the basis of lack of reticulocytosis and thrombocytopenia, as we reported previously.[8] Moreover, malaria, which is responsible for the persistence of splenomegaly in Nigerian patients,[19] has been eradicated in Sicily. The greater persistence of splenomegaly in Italian patients with S-Th (79.91%) is in harmony with previous reports for patients with S-Th.[20]

Gallstones in SCD are related to the increased catabolism of hemoglobin. A relationship between the severity of the disease and the frequency of gallstones, although highly probable, is difficult to confirm. In fact, the reported frequency of cholelithiasis varies greatly, namely from 34 to 70% in the United States,[21-23] 13% in Jamaica,[24] from 4 to 29% in Africa,[25,26] 58% in United Kingdom[27] and 8% in Saudi Arabia.[28] This variability might be a consequence of differences either in the patients' characteristics (modality of recruitment, age, ethnic group, diet) or in diagnostic methods used in the various studies.

Nonetheless, high hemolysis is the most important factor responsible for gallstones in Caucasians. In fact, the prevalence of gallstones in Italian patients who suffer from hereditary spherocytosis, a condition characterized by a low rate of hemolysis, is reported to be about 17%[29] and is, therefore, significantly lower than the 48% found in the present study. Moreover, the low prevalence of gallstones (8%) in Saudi Arabian patients probably results from the low rates of hemolysis and lower bilirubin load that are characteristic of that population.[27] It has been shown that there is a progressive age-related increase in the prevalence of cholelithiasis[20,24] and our results are in keeping with earlier reports. The higher prevalence of gallstone in patients with S-S (57.7%) than in those with S-Th (45.5%) and the younger age of patients with S-S who have gallstones as compared to those with S-Th adds another piece of evidence to the general concept that patients with S-Th suffer from a milder form of SCD than patients with S-S.

In conclusion, the present study has revealed the presence of SCD in almost all regions of Italy. The results are undoubtedly influenced by differences among the various centers that described their patients. Nevertheless, analysis of the available clinical data revealed that Italian patients suffer from a moderate form of the disease as compared to American and Caribbean patients. Our results are in harmony with reports on patients who live in other areas of the Mediterranean basin.[17] The clinical status of Italian patients with S-Th is generally better than that of patients with S-S.

Appendix

The following centers participated reporting their cases of SCD (referring physicians are given in parentheses):

Bollate, MI (A. Macagni, C. Velati); Bologna (P. Rosito); Brescia (A.G. Ugazio); Cagliari (R. Galanello); Caltagirone, CT (F. Consoli); Caltanissetta (M. Rizzo); Castellammare di Stabia, NA (G. Amendola, P. Rolando); Catania (M. Alessi); Catania (P. Samperi); Catania (S. Lombardo); Catania (V. Caruso, C. Magnano); Catanzaro (M.C. Galati); Cosenza (C. Brancati); Crotone (S. Grimaldi); Enna (E. Puleo); Firenze (P. Rossi Ferrini); Firenze (A. Lippi); Foggia (M. Monaco); Gela, CL (G. Polizzi); Genova (C. Melevendi); Genova (P.G. Mori); Lentini, SR (A. Di Pietro); Mazara del Vallo, TP (A. Adamo. A. Moceri); Messina (A. Meo); Milano (V. Carnelli); Milano (M.D. Cappellini); Milano (A. Zanella); Modena (F. Massolo); Monza (W. Monguzzi); Napoli (C. De Rosa, V Rametta); Orbassano, TO (C. Camaschella); Padova (L. Zanesco); Palermo (M. Capra); Palermo (A. Maggio); Palermo (R. Malizia); Parma (G.C. Izzi); Pavia (P. De Stefano); Ragusa (P. Rizzone); Ravenna (P. Scorza); Reggio Calabria (M. Brugiatelli); Roma (I. Bianco); Roma (A. Vania, G. Digilio); Roma (P. Cianciulli, D. Del Principe); Roma (L. Russo); S. Felice a Cancello, CE (A. Sciorio); Sassari (M. Longinotti); Sciacca, AG (C. Ciaccio); Siracusa (A. Mangiagli); Taranto (P.Mazza); Torino (L. Sacchetti); Torino (G. Degani, L. Caramellino); Varese (L. Nespoli); Verona (C. Borgna Pignatti); Verona (M. Marsia).

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GRM formulated the design of the study and was responsible for data handling, statistical analysis, interpretation and the writing of the paper. MAR participated in the design of the study, took care of the collection of questionnaires and contributed to interpretation of data. VG was responsible for handling of data and statistical analysis and contributed to drafting the paper. GS was responsible for the conception of the study, its design, funding, direct supervision and gave final approval of the version to be published. The order in which the names appear reflects the amount of work done. Particularly GRM was the principal investigator and wrote the article. Major contributions were supplied by MAR and VG. GS, as Director of the Division and supervisor has been added as last name.

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