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Diagnostic issues faced by a rare disease healthcare network during Covid-19 outbreak: data from the Campania Rare Disease Registry

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ABSTRACT

Background The aims of this study were: to investigate the capacity of the rare disease healthcare network in Campania to diagnose patients with rare diseases during the outbreak of Covid-19; and to shed light on problematic diagnoses during this period.

Methods To describe the impact of the Covid-19 pandemic on the diagnosis of patients with rare diseases, a retrospective analysis of the Campania Region Rare Disease Registry was performed. A tailored questionnaire was sent to rare disease experts to investigate major issues during the emergency period.

Results Prevalence of new diagnoses of rare disease in March and April 2020 was significantly lower than in 2019 (117 versus 317, $P < 0.001$ and 37 versus 349, $P < 0.001$, respectively) and 2018 (117 versus 389, $P < 0.001$ and 37 versus 282, $P < 0.001$, respectively). Eighty-two among 98 rare disease experts completed the questionnaire. Diagnostic success (95%), access to diagnosis (80%) and follow-up (72%), lack of Personal Protective Equipment (60%), lack of Covid-19 guidelines (50%) and the need for home therapy (78%) were the most important issues raised during Covid-19 outbreak.

Conclusions This study describes the effects of the Covid-19 outbreak on the diagnosis of rare disease in a single Italian region and investigates potential issues of diagnosis and management during this period.

Keywords Campania region, Covid-19, Italy, patient registry, rare diseases

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Introduction

The severe acute respiratory syndrome coronavirus-2 (SARS-Cov-2) has been declared a pandemic by the World Health Organization, emerging as a global threat due to the high transmission rate of the virus and the high number of deaths.[1,2] The presentation of Covid-19 is extremely heterogeneous, ranging from the absence of symptoms to severe disease, including three phases (i.e. viral infection, pulmonary phase, hyperinflammatory illness/systemic phase).[3–6] The exponential demand for hospitalization and emergency care has suddenly changed the priorities of healthcare systems around the world, and many hospitals have been dedicated to Covid-19 patients, in part or as a whole.[7,8] At the same time, routine outpatient management of patients with chronic and rare diseases has been suspended in most hospitals.[7–9]

With a prevalence of less than 1 in 2000 people, rare diseases affect more than 300 million people worldwide.[10] Compared with common diseases, such as diabetes or coronary artery disease, each rare disease affects a small number of people with specific issues related to their rarity, including the delayed clinical diagnosis, the paucity of expertise centers that often are at a great distance from patients' home, the absence of specific therapies,[10,11] etc.

In response to the growing Covid-19 pandemic in Italy, the Italian government has imposed a national lockdown, limiting the movement of the population except for necessity, work and health circumstances. In Italy, the national lockdown started on 9 March 2020 and was extended several times, until 3 May 2020.

The effect of lockdown is expected to have a significant impact on the rare disease healthcare network and its capacity to diagnose and manage patients. Nevertheless, there is a lack of data in the literature on this topic.

The aims of this study were: to investigate the capacity of the rare disease healthcare network in Campania (southern Italy) to diagnose patients with rare disease during the outbreak of Covid-19; and to investigate the potential issues regarding patient diagnosis faced by rare disease healthcare experts in Campania.

Methods

Study design

Since 2001, Italy has had a structured system to provide health care to patients with rare diseases, based on the 2001 rare disease ruling (*Decreto ministeriale n. 279*), which promotes the development of Rare Diseases Registries (RDR) at a regional level, and linked to the National Registry of Rare Diseases.[12]

To describe the impact of the Covid-19 pandemic on the diagnosis of patients with rare diseases, a retrospective analysis of the Campania Region RDR (CRRDR) was performed.

The CRRDR is part of a consortium called 'AREA VASTA', which includes eight Italian regions (Provincia Autonoma Trento, Provincia Autonoma Bolzano, Veneto, Emilia Romagna, Umbria, Campania, Puglia and Sardegna) and is coordinated by Veneto Region. All the entities included in the list of rare diseases of the national health system are present in the database with a specific code ('R' code) and clustered in 16 macro-groups (i.e. rare infective disease, rare metabolic disease, rare malformations, etc.).[12,13] This registry includes demographic and clinical information routinely collected by physicians of the Campania rare disease network and authorized to access the system by hospital managers (https://malattierare.rve.overnetwork.it/). The acquisition and management of the data comply with the EU 2016/679 General Protection Data Protection Regulation.[14]

To investigate major and minor issues faced by the Campania rare disease network during the Covid-19 outbreak, a specific questionnaire was designed by GL, PC and SI (Table 1).

Our research protocol adheres to the principles of the Declaration of Helsinki and its amendments and has been approved by the Ethical Committee of the AO Colli/Vanvitelli University (prot. n°AOC-0013766-2020; 08/05/2020).

Study population and methodology

All subjects with certified rare disease were included in the CRRDR. We have retrospectively analyzed all the new diagnoses obtained in the first four months of 2020 (January–April) and then compared the results with the diagnoses performed in the first four months of 2019 and 2018. Furthermore, a sub-analysis according to different rare disease macro-groups and/or for single disease/code was performed. Particular attention was given to the number of certificates of a rare disease issued in the first four months of 2020, comparing it with the first four months of 2019 and 2018.

A dedicated questionnaire (Table 1) was designed and sent by email to the physicians of the Campania rare disease network. To detect challenges in the diagnosis of rare diseases during the first four months of 2020 due to the Covid-19 pandemic, the questionnaire was sent only to physicians who issued a high number of certificates for rare disease in 2019 (i.e. > 5). Following this protocol, the questionnaire was sent to 98 specialists and 82 were completed. To facilitate compilation and to avoid misunderstanding, all the questions had binary or a limited set of options.

Table 1 Answers of the questionnaire sent to the physicians included in the Campania rare disease network

Questions	*Answers*	*No. (%)*
1. Have you issued a certificate of rare disease since March 1st?	Yes	47 (57.3)
	No	35 (42.6)
2. Were there any Covid-19 patients among those who received the certificate of rare disease?	Yes	78 (95.1)
	No	4 (4.9)
3. What group of rare disease do you certify? (please mark one or more of the following)	1. Infectious and parasitic diseases	0 (0)
	2. Neoplasms	6 (7.3)
	3. Endocrine and nutritional disorders	16 (19.5)
	4. Metabolic diseases	11 (13.4)
	5. Immunity disorders	7 (8.5)
	6. Diseases of the blood and blood-forming organs	13 (15.8)
	7. Diseases of central and peripheral nervous system	13 (15.8)
	8. Diseases of the sense organs	6 (7.3)
	9. Diseases of the circulatory system	3 (3.6)
	10. Diseases of the respiratory system	7 (8.5)
	11. Diseases of the digestive system	3 (3.6)
	12. Diseases of the genitourinary system	8 (9.8)
	13. Diseases of the skin and subcutaneous tissue	9 (11.0)
	14. Diseases of the musculoskeletal system	8 (9.8)
	15. Genetic malformations, chromosomal disorders and genetic syndromes	16 (19.5)
	16. Certain conditions originating in the perinatal period	5 (6.1)
4. Has the Covid-19 pandemic limited the diagnostic capacity of your center?	Yes	78 (95.1)
	No	4 (4.9)
5. Which activity was the most affected during the Covid-19 pandemic? (please mark one or more of the following)	Access to therapy	30 (36.6)
	First access/in-depth diagnosis	66 (80.5)
	Follow-up	59 (72.0)
	None of these	0 (0)
6. What were the most challenging aspects of the healthcare during the Covid-19 pandemic? (please mark one or more of the following)	Lack of drugs	1 (1.2)
	Lack of healthcare workers	24 (29.3)
	Lack of PPE	49 (59.8)
	Lack of Covid-19 guidelines	41 (50.0)
	None of these	6 (7.3)
7. Can your patients discontinue therapy without experiencing a clinical worsening?	Yes	17 (20.7)
	No	65 (79.3)
8. Do you think that home therapy (when available) is a possible alternative for your patients?	Yes	64 (78.0)
	No	18 (22.0)
9. Have you recommended home therapy (when available) to your patients?	Yes	60 (73.2)
	No	22 (26.8)
10. Have any of your patients asked to discontinue his/her therapy?	Yes	12 (14.6)
	No	70 (85.4)
11. Have any of your patients asked for home therapy?	Yes	50 (61.0)
	No	32 (39.0)

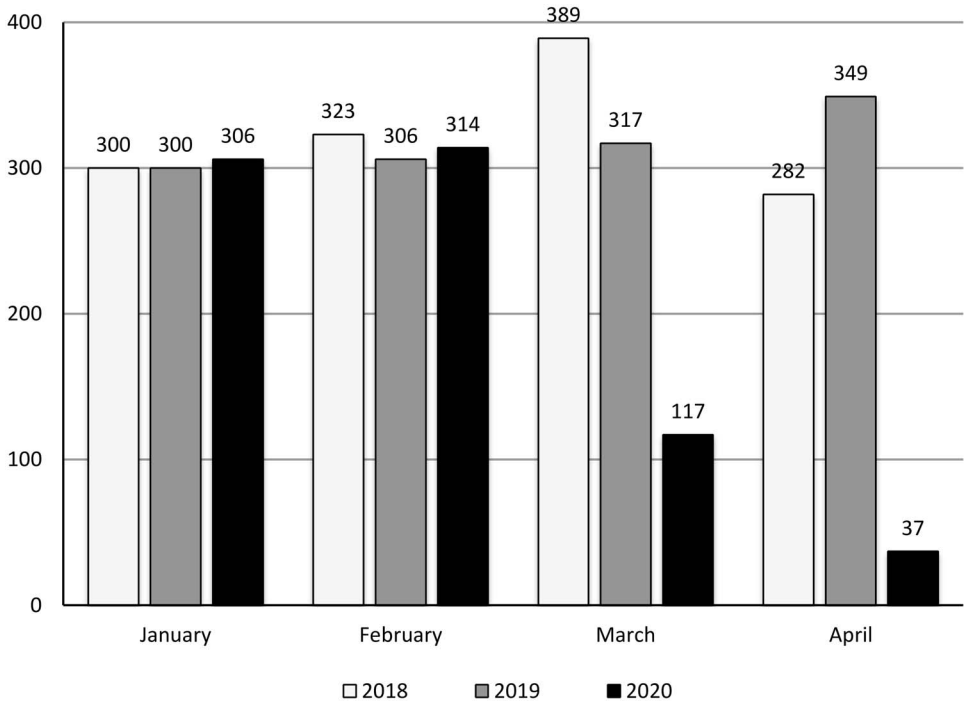

Fig. 1 Number of certificates issued in the first 4 months of the years 2018, 2019 and 2020.

Statistical methods

Descriptive statistics were used to analyze different time-periods of CRRDR and analyze answers to the questionnaire from the specialists of the rare disease network. Comparison of the number of certificates between time-periods was made by means of Poisson test. A *P*-value lower than 0.05 was considered statistically significant. Data were analyzed using R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

The effect of Covid-19 outbreak on Campania Rare Disease Network: comparison of the first four months of 2020 versus 2019 and 2018

The prevalence of new diagnoses of rare diseases (i.e. certificates entered in the CRRDR) in the first four months of 2020 was significantly lower than 2019 (774 versus 1272; $P < 0.001$) and 2018 (774 versus 1294; $P < 0.001$) (Fig. 1). This difference is mainly related to significantly fewer diagnoses clinched in March and April 2020, as no significant differences were found in January and February of the same year, compared with those performed in 2018 and 2019. In March and April 2020, 117 and 37 diagnoses of rare disease were made. These numbers were significantly lower than 2019 (117 versus 317 in March; $P < 0.001$; 37 versus 349 in April; $P < 0.001$) and 2018 (117 versus 389 in March; $P < 0.001$; 37 versus 282 in April; $P < 0.001$).

Among the 11 hospitals included in the rare disease Campania network, we described the results of the six with the most certificates in the first four months of 2018 and 2019, to reduce variability related to the low number of diagnoses performed in the remaining hospital. In the first four months of 2020, except for Cardarelli hospital, all the hospitals had fewer certificates compared with 2018 and 2019, as shown in Fig. 2A. However, focusing on April, the decreased number of diagnoses in 2020 occurred for all six hospitals within the Campania network (Fig. 2B).

Furthermore, we analyzed the number of certificates issued in the first four months of 2020 for each rare disease macro-group and compared it with 2019 and 2018 (Fig. 3A). Group 7 (diseases of central and peripheral nervous system) was the most prevalent macro-group in the 3-year period. Considering the first four months of the years, for all the 16 macro-groups, the number of certificates was lower in 2020 than in 2019 and 2018, with some exception (i.e. Group 11 [diseases of the digestive system]: 25 in 2020 versus 23 in 2018; Group 6 [diseases of the blood and blood-forming organs]: 91 in 2020 versus 89 in 2018; Group 3 [endocrine and nutritional diseases]: 76 in 2020 versus 37 in 2018). However, focusing on the month of April (Fig. 3B), for all the macro-groups, the number of certificates in 2020 was lower than 2019 and

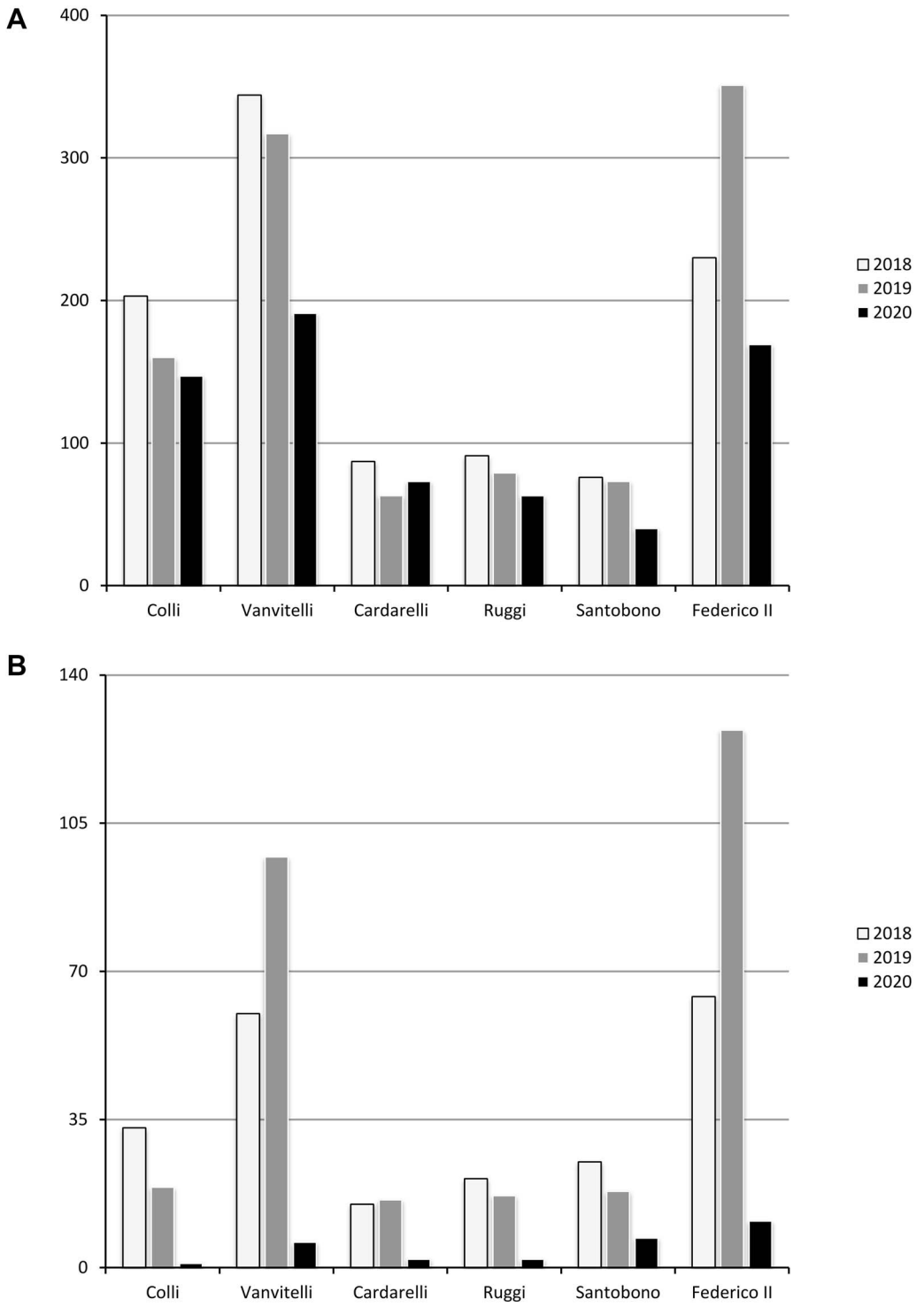

Fig. 2 (A) Number of certificates issued in the first 4 months of the years 2018–2020 among the six hospitals with the largest activity of certification. (B) Number of certificates issued in April of the years 2018–2020 among the six hospitals with the largest activity of certification.

2018, and in three groups (groups 3 [endocrine and nutritional diseases], group 8 [diseases of the sense organs] and group 11 [diseases of the digestive system]), no certificates were entered in the CRRDR. In April 2020, more than 10 certificates were issued in group 7 alone (diseases of central and peripheral nervous system).

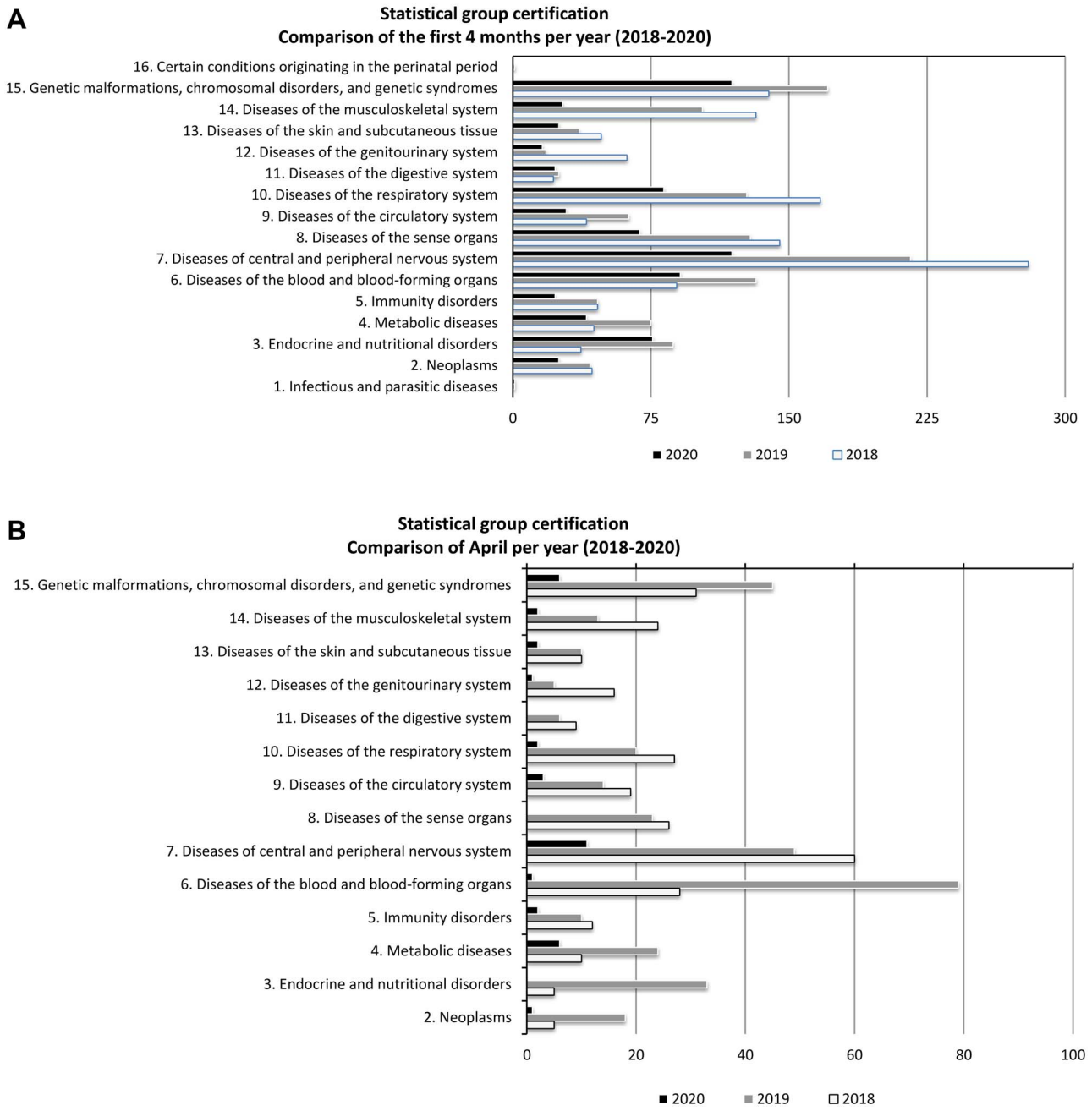

Fig. 3 (A) Number of certificates issued in the first 4 months of the years 2018–2020 for each rare disease macro-group. (B) Number of certificates issued in April of the years 2018–2020 for each rare disease macro-group.

Moreover, the number of certifications issued in April of the 3 years was also surveyed. As reported in Supplementary Table S1, we considered the rare diseases with the highest number of certificates in April 2018 and 2019 and compared it to April 2020. Overall, the number of certificates in April 2020 was significantly lower than April 2018 (28 versus 327) and 2019 (28 versus 299), and this finding was consistent for all the rare diseases (except for isolated deficiency of growth hormone: 3 in April 2018 versus 5 in April 2020).

A survey on the effect of Covid-19 outbreak on diagnosis and management of rare disease in Campania

The response rate to the survey administered to the rare disease experts of the Campania network was 83.7%. The questionnaire was sent to 98 specialists and 82 completed questionnaires were returned. The answers to the questionnaires are reported in Table 1. Diagnostic success (95%), access to diagnosis (80%) and follow-up (72%), lack of

Personal Protective Equipment (PPE) (60%), lack of Covid-19 guidelines (50%) and the need for home therapy (78%) were the most important issues raised during the Covid-19 outbreak.

Discussion

Covid-19 outbreak: the challenge of rare disease

The Covid-19 pandemic has created ongoing challenges for health systems worldwide, and in Italy, the decentralization and fragmentation of healthcare services have limited interventions and effectiveness.[1–8] Furthermore, despite the steady march of progress in management strategies in the pre-vaccine era, the only effective measure to counteract the spread of Covid-19 was represented by regional or national lockdown.[15] Nevertheless, the reorganization of health systems, the national lockdowns and the fear of SARS-Cov-2 infection have kept most patients away from hospitals and have had negative effects on the diagnosis and management of acute and chronic disorders.[2,7,8,9] For example, during the Covid-19 pandemic, there have been fewer hospitalizations for acute myocardial infarction[16] and a significant delay in the routine care for chronic disease, resulting in an increased number of complications.[17–19]

Lack of knowledge and expertise often makes the diagnosis of rare disease a challenge, and an average time of 6 years from symptom onset to a specific diagnosis has been reported.[20] Thus, patients with a rare disease often face a 'diagnostic odyssey', typically receiving multiple and inconclusive diagnostic tests, misdiagnosis and incorrect treatments, that profoundly impact psychological wellbeing, clinical stability and socioeconomic costs.[21–23] The significant diagnostic delay often results in disease progression, resulting in an increased risk of disease complication and reduced efficacy of etiological treatments.[24]

Covid-19 outbreak: the effect on the rare disease network in Campania

Covid-19 had a negative impact on the Campania Region's rare disease network, as seen in the CRRDR database. In particular, we observed a significant decline in certificates issued in March and April 2020 compared with the same two months of 2019 (less than 63 and 90%, respectively). These findings underline the real impact of Covid-19 on the diagnosis of rare diseases. As a consequence of the lockdown period, the conversion of many hospitals into Covid-19 dedicated units and the postponed 'elective' care, all 16 rare disease macro-groups experienced disruptions in diagnosis and management.

At the same time, scrutinizing the questionnaire uncovered a series of issues raised by the network specialists. The most affected activity was the 'first-access'. Specifically, the first evaluation of a patient with suspected rare disease was often postponed as a consequence of the less outpatient activity and elective care, or because patients refused the hospital admission for the fear of Covid-19 infection.

A national survey[25] was conducted by UNIAMO (*Federazione delle Associazioni di Persone con Malattie Rare d'Italia*, 23rd March–05th April) in collaboration with the 'Istituto Superiore della Sanita', about the needs of people with rare disease during the pandemic. In their survey, more than half of the interviewed patients suspended treatment against doctor's orders. In contrast, in our survey, most of the patients did not stop treatment. This difference is probably linked to the inconsistent way in which the answers were obtained (in the UNIAMO survey, they were completed by the patients themselves, while in the present survey, this was done by the healthcare professionals). Nevertheless, most of them preferred home therapy and, whenever possible, it was also encouraged by their doctors.

Home therapy/home delivery was assured for all patients, children and adults, requiring hospitalization for regular intravenous infusion (i.e. lysosomal storage disease). Indeed, home therapy was approved by the Italian Medicines Agency, providing the extension of therapeutic plans and encouraging home therapy when possible. In addition, a helpline was set up to assist patients with rare disease and immunosuppression.

Limitations

This work presents several limitations. First, these results represent a narrow window into the region's healthcare and should now be compared with other experiences. Second, other factors, potentially responsible for a fall in certificates in March/April 2020, have not been investigated. Indeed, fewer certifications can be partially related to administrative obstacles during the Covid-19 pandemic (i.e. the trouble updating the rare disease registry). Third, the results of extraordinary measures (telephone support and home therapy/home delivery models) were not considered in the present study. Finally, not all the rare disease experts inside the regional network administered the questionnaire. However, more than two-third answered the questionnaire, and we think this can be representative of the regional situation.

Conclusions

In conclusion, this study depicts the effects of Covid-19 outbreak on diagnosis and management of rare diseases in

a single Italian region. There were fewer diagnoses of rare disease during the outbreak period, and this was observed for all the hospital networks, the macro-groups and single rare diseases. A number of issues were raised (including diagnostic capacity, access to diagnosis and follow up, lack of PPE, etc.) by rare disease experts during the Covid-19 outbreak. Extraordinary measures, including telephone support and home therapy/home delivery, have been taken during the emergency phase, representing an example of how healthcare can potentially respond to the Covid-19 outbreak.

Supplementary data

Supplementary data are available at the *Journal of Public Health* online.

Authors' contributions

G.L., S.I., P.E., G.S., G.A., V.O., E.M. (Enrica Menditto) and P.C. contributed to the conception and design of the work. G.L., S.I., P.E., C.D.S., I.L., M.C., M.M., F.F., M.G., G.D.M., S.E., G.S., G.A., V.O., E.M. (Enrica Menditto) and P.C. contributed to the acquisition, analysis or interpretation of data for the work. G.L., S.I., E.M. (Emanuele Monda), P.E., G.S., G.A., V.O., E.M. (Enrica Menditto) and P.C. drafted the manuscript. All the authors critically revised the manuscript. All gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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Conflict of interests

The authors declare that they have no competing interests.

Data availability statement

All data are incorporated into the article and its online supplementary material.

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