Retrospective Study

THE IMPORTANCE OF TERRITORIAL EMERGENCY MEDICINE THE ROLE OF ITALIAN SET-118 DURING THE COVID-19 PANDEMIC, A MULTIDISCIPLINARY APPROACH TO FACE THE NEXT PANDEMIC CATASTROPHE

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ABSTRACT

In Italy, patients in life-threatening emergencies are primarily managed by the 118 emergency service and pre-hospital medical facilities. Taking charge begins with the centralized reception of calls, which allows the dispatch of medical supplies and emergency medical assistance on-site before hospital care. The 118 services ensure that medical and paramedical units are often the first on-site. At the same time, the professional skills of the sending doctor are essential to ascertain the patient's clinical condition, preserve their vital functions, ensuring appropriate emergency health care in nearby hospital facilities. During the COVID-19 pandemic, the first aid service has shown critical issues: extremely limited medical facilities in some areas of the country, fewer volunteers and doctors, hospital reorganization, limited funding, and poor skills of "first on scene" responders. This has spotlighted equal healthcare opportunities for all and the need for more qualified medical training, especially for emergency healthcare personnel, such as assistants, paramedics, and drivers. COVID-19 has prompted an improvement in the efficiency of the system, with a plan to achieve the goals and the implementation of an emergency services network with different degrees of emergency healthcare management. In our experience, following the COVID-19 pandemic, the level of emergency healthcare has opened the need to operate with high-level equipment managed by highly qualified emergency personnel, also considering the issues related to post-pandemic problems, such as the "long COVID" syndrome. This paper has highlighted the strategic importance of 118 at the national level during the recent pandemic, highlighting the efforts and countermeasures adopted by the SET 118 of the city of Taranto.

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INTRODUCTION

This study describes the territorial emergency healthcare provided by the 118 National Units as a key strategic actor in emergency medicine in the field; however, even today, local authorities or the central government do not fully understand the importance of these services. Furthermore, there are few links between academics and the 118 system in participating in data sharing. Therefore, to be effectively ready for any circumstance that may arise in the future, it is necessary to promote dynamics to optimize this practice both qualitatively and quantitatively (1).

The COVID-19 pandemic has represented one of the greatest challenges for global health systems in recent years. In fact, the sudden appearance of a large number of patients affected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has revealed the degree of unpreparedness of the Italian health system for such a dramatic event (2).

Healthcare workers are faced with multiple fronts simultaneously: helping numerous patients with a new, highly contagious disease, addressing the lack of care for patients with chronic diseases, emergency conditions, or other health conditions and diseases, and limiting the risk of exposure to SARS-CoV-2 (2, 3).

In the early months of the COVID-19 pandemic, healthcare workers had little certainty to rely on: the clinical course of patients was highly unpredictable and the greatest concern was the transmissibility of the pathogen. Early reports suggested that over 40% of hospitalized patients would require supplemental oxygen and up to 15% could require mechanical ventilation (1-3), procedures for which there is an established risk of disease transmission to healthcare workers through infectious aerosols (4).

Infection and death rates among healthcare workers, doctors, nurses and paramedics, caring for patients with COVID-19, reached shocking values in the first months of the pandemic (5, 6). This risk of infection was also implemented by the extreme difficulties of providing care in a pre-hospital environment: these areas were difficult to control, patients were undifferentiated, personal protective equipment (PPE), resources were limited and information was scarce.

During the lockdown period, the number of recorded home infection events also increased significantly (5, 6). However, there is little scientific data on the impact of the lockdown on COVID-19-related out-of-hospital deaths. Major changes made in the EMS organization during the pandemic did not cause a significant increase in major trauma mortality in our large study population (5-7).

Context

The Taranto Provincial Operations Center "118" Territorial Emergency System (SET 118) is the publicly funded provider of ground ambulance and medical/paramedic services for the municipalities of the city of Taranto and its provinces in the Puglia region, which collectively comprise a mixed suburban and rural geography of 2467.35 km2, with a population of approximately 600,000 residents. The service employs over 700 paramedics and primary and advanced care physicians who operate a total of 65 ambulances and eight rapid response units during peak hours (Fig. 1) (8).

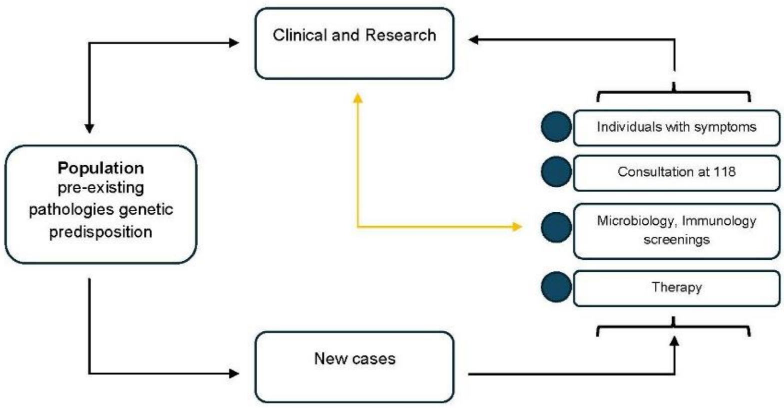

Fig. 1. *The gate model proposed by Taranto's SET 118 assigns a special role of protection of the territory both to the 118 doctors and to the GPs, according to the Anglo-Saxon logic of entrusting the specialist reception unit of the hospital: the GPs and the doctors of the 118 have been proposed as the diagnostic vanguard to face and solve the first problems acting as filters before being directed to specialist cares. By this way it was emphasized a new management procedure with the intent of coordinating territory care and hospital care for implementing a systematic therapeutic plan.*

The province of Taranto is geographically divided into 6 health districts, each with a centralized headquarters from which crews start their shift in a "hub-and-spoke" and are then required to move to the territories or points requested by calling 118.

Ambulances are staffed by two paramedics and a doctor in primary care paramedic (PCP) or advanced clinical practitioner (ACP) configuration, and rapid response units are equipped with a single PCP. On average, 118 can respond to approximately 130,000 emergency calls per year (8).

As of April 2020, 118 was operating under a declared state of emergency throughout Italy, while SET 118 Taranto mobilized a joint union and management task force under the Incident Management System framework to develop local rescue.

Our task force included representatives with experience in medical and paramedical education, occupational health nurses, and safety professionals, with an immunology team serving as a liaison to the Emergency Operations Center and the Taranto Central Health Department service response to the crisis (8).

SET 118 Taranto continued to be one of several “hotspots” in the province for the care of community transmission of COVID-19, in part due to essential emergency personnel and territorial units (8, 9).

Interventions, program and objectives

In April 2020, in the Puglia region, the local hospital SG Moscati and the 118 SET, were operating in a state of emergency for which they mobilized a joint union and management task force establishing a filter unit under the 118 management system framework to develop emergency first aid prior to hospital admission.

The task force included paramedics, nurses and physicians, medical immunology researchers and service operations with the leadership acting as a link with the Emergency Operations Center of the Province and the Region (9). Over 1500 patients were admitted to our COVID-19 SET 118 emergency unit of the SG Moscati Hospital in Taranto from March 2020 to November 2020. The majority were male (61%), 17 deceased (5%) with an average age of 72 years.

In that period, over 10,000 calls were collected by the Pre-hospital Health Service 118 operating in the province of Taranto. Patients were managed who reported symptoms attributable to possible respiratory diseases or who claimed to have had contact with people with suspected or confirmed SARS-CoV-2 infections. With regard to gender: 40.96% of the calls came from female patients while 59.04% involved male patients (9, 10).

The reported symptoms were fever, cough, general malaise, difficulty breathing, headache, cold, sore throat, conjunctivitis, alterations in taste and/or smell, gastrointestinal symptoms; a large percentage of these reported having had contact with patients affected by SARS CoV-2 without showing symptoms of infection. Furthermore, patients who reported symptoms were divided into different age groups: 0-9 years, 10-19 years, 20-34 years, 35-59 years, 60-69 years, 70-79 years, 80-89 years, ⩾ 90 years.

The dynamic development of hospital preparedness and the SET 118 response were essential to ensure the right effectiveness of healthcare due to COVID-19, to reduce the spread of infection and prevent hospitals from being overwhelmed due to the large number of severely ill patients infected with COVID-19 (8-10).

A key consideration was the resilience of 118 and its ability to adapt and manage beyond what was normally possible to provide pre-hospital clinical treatment, as COVID-19 resulted in a short period of rapid growth in demand. Therefore, the Taranto SET 118 was required to take proactive measures to manage emergency care requests, identify gaps in territorial intensive care and identify maximum case admission capacities (8, 9).

Our model used data that included city performance indicators such as types of daily emergency calls, clinical priority level, ambulance types (Dual/ALS/BLS), and EMT/paramedic or physician crew data that were often collected during the previous non-pandemic period.

Second, we addressed possible limitations found by other Covid studies that may include the recognition and reporting of early signs and parameters of symptoms (fever, cough, difficulty breathing, loss of taste and smell, extreme tiredness) (8-11).

The overall program goal for SET 118 Taranto was primarily to prevent COVID-19 infections in the community while continuing to ensure high-quality care while minimizing the risk of hospital congestion. We identified three specific program goals: 1): limit physician and paramedic exposure to the virus within the service to the extent reasonably possible; 2): ensure hospital services and safety through frequent exposure to high-risk patient types and procedures; 3): provide high-quality resuscitation care to critically ill patients, including performing aerosol procedures where they were typically indicated while avoiding overloading hospital care units (8). In this respect, we tried to solve the underlying medical intervention and logistics problems based on some previous studies and our experiences before the COVID-19 pandemic.

The first step was to estimate and predict the travel or response times of ambulances using a coordinated system of information that changes between the camps and the Central Operations Quarter (COQ).

A specific intervention time interval was established based on the relationship between the number of calls or counts and the duration (the time elapsed between calls) with the data collected and the symptoms described by the patients. Between each call and intervention, ambulances and responders were dispatched to each event, recording the critical times of each intervention.

An innovative operational plan

At the beginning of the pandemic, the regulatory bodies that govern SET 118 practices in Puglia issued a regulation that recommended limiting ordinary tasks in all but extraordinary circumstances. Included in this file were: limiting the use of nebulized drugs, continuous positive airway pressure, bag-mask ventilation, and high-flow oxygen administration, among others (8-11).

The SET 118 emergency response system to the COVID-19 pandemic consisted of multiple interconnected components, such as: the creation of a special pre-hospital COVID-19 unit that functioned as inpatient clinical treatment, the creation of an emergency management plan that included the infection prevention and control program, the creation of a special research unit to collect data, numbers, and scientific information to support clinical case management, coordination of communications, laboratory and diagnostic services (8-11).

We then conducted a systematic review of the emerging literature by implementing a large medical research activity that allowed us to come out with new diagnostic and therapeutic methodologies.

The final results allowed us in a short time to reach a complete picture regarding the pleiotropism of SARS-CoV-2 and to describe recommendations for the management of COVID-19, cardiopulmonary resuscitation and preventive measures in patients with confirmed or suspected COVID-19 and in the general population.

Through this research work we were able to draw up a clear protocol that informed and prepared our operations both in the field and in the COVID-19 unit.

Following these recommendations, we structured the team to implement most of them, with the notable exception of the use of video laryngoscopes for intubation, which is not standard in our service and daily procedure.

We drew inspiration from best human factors practices used by high-performing emergency medical service systems in Europe, such as the use of pre-procedure checklists and crisis resource management principles. Our task force developed the operating concept and procedures for the team through consensus building based on emerging literature and best practice recommendations as described above. This was achieved through teamwork that required regular in-person meetings, frequent engagement with ambulance staff and frontline paramedics and supervisors from other departments (intensive care, pulmonology and infectious disease) within the paramedic service, and simulation of the proposed procedures to identify potential points of failure.

The SET 118 COVID-19 pre-hospital filter unit

The COVID-19 Special Unit we built is equipped with a negative pressure system to handle the immense flow of patients entering the 24-hour SG Moscati Hospital. Unlike normal operations, the Unit's crews were deployed outside of normal dispatch procedures and were autonomous in triaging patients for care based on physical and diagnostic parameters to identify high-acuity patients likely to require initial aerosolization and medical care.

The crew was alerted via text messages from our ambulance or field team for calls involving "clear immediate threat to life" criteria, including dry cough, fever, cardiac arrest, altered level of consciousness, severe respiratory distress, and existing comorbidities, among others.

Physicians and nurses in the admissions room could also request a COVID-19 Special Unit crew to respond to the scene. The COVID-19 Special Unit was a "first-in" response that arrived promptly. The medical crew discussed the risk assessment with the paramedics already present while it was anticipated that patients would require the required full testing and diagnostic procedure.

A special "COVID zone" was created divided into two designated wings, "area A" where only our special staff were present during patient care and a "B or hot zone" area where ICU patients with PPE transported by air would remain and require high flow O2 masks.

Once the aerosolization procedures were completed, the staff on the scene would assist with mask removal, and the patient would be transported to the central hospital wards. In COVID-19 SET 118, the physician in charge was responsible for liaising with the receiving facility staff to arrange the transfer procedure along with a detailed care plan before the patient was removed from the facility (Fig. 2, 3).

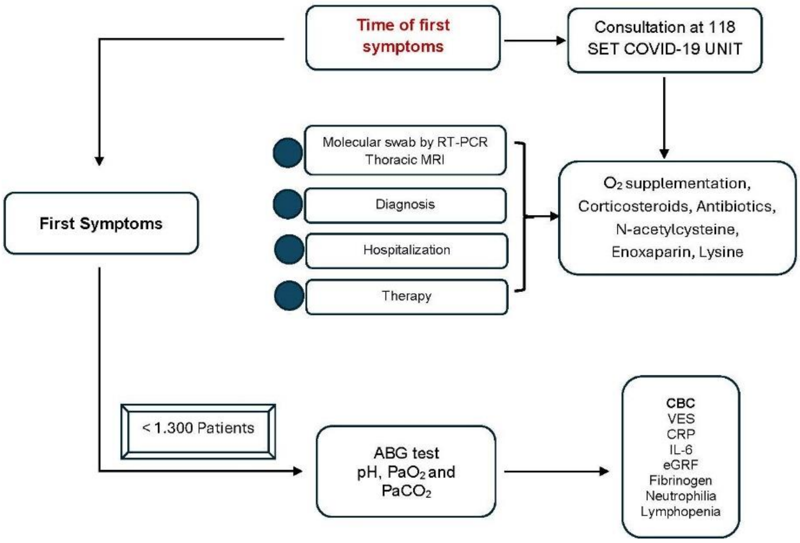

Fig. 2. *The above algorithm allowed the 118 SET to reach tremendous results, proceeding with multi-disciplinary approaches by setting up a multi-centered therapy that combined O2 support, antioxidants, antiretroviral, cortisone, and antibiotics to arrest systemic inflammation and prevent multi organs decay, a model that was posing the base of an epidemic preventing action for the upcoming winter season.*

Prehospital emergency care of suspected COVID-19 patient with acute respiratory failure

Objective

Ensure the patient classified as a suspected or full-blown case with an initial clinical picture of acute respiratory failure and/or shock the appropriate and continued emergency therapeutic support during the phases of protected transport and temporary management pending the taking charge of the dedicated hospital units.

Methodology

At home and in a mobile station (ambulance) SET-118 → acute respiratory failure → therapeutic protocol

Oxygen therapy, as needed (SpO2> 90%):

- low flow (P/F > 300 mmHg): with nasal goggles: 2 - 4 L/min
- high flow (P/F < 300 mmHg): with face mask with reservoir: 15 L/min

Non-Invasive Mechanical Ventilation (Sp02< 90% or P/F < 200 mmHg + severe dyspnoea, use of accessory respiratory muscles - sternocleidomastoid, scalenes, paradoxical breathing-, RR > 35 breaths/min, pH < 7.35, pH> 7.2, Kelly 1-2) → CPAP: 5 - 10 cm H2O, with FiO2 of 60 - 90%

In more severe cases

In the presence of severe hypercapnia, altered mental status, hemodynamic instability, invasive mechanical ventilation IMV → ETI is indicated.

If the clinical picture compatible with bilateral interstitial pneumonia:
dexamethasone: 6 mg iv (associated with gastroprotection with pantoprazole 40 mg iv)
acetylcysteine f1300 mg iv: 2 flev in 250 ml of saline
enoxaparinafl: 1 fl4000 IU sc (in the absence of specific contraindications)

Intravenous drip with 5% glucose solution for nutritional purposes, in case of prolonged hospitalization.

Where an emergency vehicle with a non-medicalized but nursed crew intervenes on an unstable COVID-19 patient, the 118 Operations Center can guarantee remotely, through the CO118 doctor or even through the SET doctor specifically dedicated in service at the CO118 to carry out operations of "medical control online", real-time medical support for the administration of emergency therapy.

Fig. 3. *The admission to the pre-hospital unit was created to avoid the overload into the hospital of the Taranto areas. The admission phases were based on the clinical condition of each patient at the moment of 118 COVID-19 Unit acceptance. Based on symptoms and ABG parameters the therapies could be delivered home or organized and performed at the site.*

Measures, analysis, and research, what we have achieved

We did not find much evidence on how measures were managed by area and population as the pandemic progressed, although some researchers and laboratories have already reported changes during the evolution of Covid and during the advanced stages of the pandemic.

Therefore, our evaluation, screening, and research program was based on a manual review of all patient electronic health records (ePCR) data, convincing laboratory results conducted with a careful peer-review search of published works in viruses, microbiology, and immunology regarding similar viral infections. The data we focused on most was the percentage of calls involving high-risk COVID-19 with the intention of predicting, preventing and treating COVID-19 infection (11, 12) .

To provide a contextualized basis for comparison, we manually examined PCRs for all admissions where COVID-19 patients were performed in the first and second waves (February-May 2020 and September-November 2020) of the pandemic, which led to the drafting of articles for international publication. We subsequently continued to explore both the scientific hypothesis related to the unique pleiotropism of SARS-CoV-2 and to create a new RT-PCR diagnostic method. To do so, a collaboration was established with several departments, laboratories, and universities (national and international), such as Aldo Moro University of Bari (Italy), Phan Chau Trinh University of Medicine (Vietnam), and Lincoln University (Oakland, California, USA). This teamwork allowed us to collect critical information that gave us a clearer picture of the situation.

SARS-CoV-2 pathogenic traits emerged slowly, helping us to assess a faster diagnosis and realize a more effective therapy. The results confirmed the distinctive patterns of the virus' mode of infection and its ability to evade immune surveillance and host responses (11, 12). From our research, we learned about gender-based differences in COVID-19: male patients were at higher risk of developing severe disease with increased mortality rate, and the time to intervention was crucial, 36 hours maximum from the first signs.

The results of retrospective cohort studies from March to November 2020, which assessed the mortality rate in over 1300 ICU patients with confirmed SARS-CoV-2 infection, reported a higher mortality rate in male patients (12.5%) compared to female patients (9.6%) (8, 9).

We promptly highlighted the phenomenon known as “happy hypoxia”, coined by J. Couzin-Frankel (8,13,14). “Happy hypoxia” was an event that many patients experienced characterized by a sudden decline saved by high-flow oxygen support performed in intensive care. The etiopathogenesis was then related to a severe endothelitis, considered the main causal factor affecting the microcirculatory mechanism, followed by a silent and rapid necrosis process linked to a generalized increase in uncontrolled inflammatory processes leading to microvascular thrombosis, coma, and then death (8, 13, 15). By monitoring many patients who showed rapid deterioration, we started to implement the use of arterial blood gas (ABG) analysis: it helped us to clarify some specific dynamics of the infection functional to the adoption of more effective therapies and treatments. The ABG results were atypical, a sign of an acute hypocapnic respiratory state accompanied by a hypoxemic condition with a compensatory alkalosis.

This picture suggested a progressive pulmonary microembolism, specular to an ongoing internal hypercoagulability with endothelial activation due to an uncontrolled increase in proinflammatory cytokines, the infamous "cytokine storm" (16, 17).

The hypoxemic state has been described as an increase in minute ventilation leading to an uncontrolled hypocapnia, due to the rapid diffusion of CO_2 into the tissues, CO_2 moving about 20 times faster than O_2. This allowed us to understand the pathoanatomical and pathophysiological basis of COVID-19 respiratory failure, characterized by the presence of progressive and widespread damage to multiple organs and tissues and alveoli with interstitial thickening, deep vein thromboembolism, and impaired gas exchange. This scenario was often accompanied by atelectasis and lung consolidations, visible on CT images with typical ground-glass opacities (8,9). Eventually, the combination of ABG analysis (partial saturation level of oxygen and carbon dioxide - PaO_2 and $PaCO_2$) and CT proved to be a better tool in diagnosing COVID-19 than RT-PCR swabs alone (8, 9).

The complete blood count of COVID-19 patients performed immediately after ABG tests indicated the presence of an infectious-inflammatory condition with involvement of the lungs, heart, and kidneys. The most common picture was a high total white blood cell count (WBC > 10,000 cells/mcL), with marked neutrophilia and lymphopenia.

Laboratory results confirmed low levels of eGFR and 25OH-vitamin D, increased levels of troponin, IL-6, D-dimer and ESR and an increased level of fibrinogen. At that time, we were able to highlight a secondary phase of the infection triggered by aggressive bacteria, which was later confirmed by other teams worldwide.

The rapidity of multiorgan involvement with the contextual septic course was related to the presence of several pathogens identified in the BALF and blood culture, such as Klebsiella spp, Candida albicans, Aspergillus, Pseudomonas spp, which have proven to be a prerogative feature of the final phase of SARS-CoV-2 infection (8, 9).

The mechanism of Sars-CoV-2 infection affects all cell types (epithelial, neuronal and myocyte) via the angiotensin-converting enzyme-2 (ACE2), followed by the cleavage of S by the transmembrane serine protease 2 (TMPRSS2). This explains the multiplicity of symptoms that characterize COVID-19 disease (8, 9, 13, 15, 16, 18).

Our investigation allowed us to explain a very unusual phenomenon consisting of the aberrant increase in erythroid progenitors and an anomalous decrease in platelet circulation in critical hospitalized cases and after receiving the vaccine injection (18). Such observations, together with hypoxia, hypocapnia, alkalosis, iron deficiency anemia, and coagulopathies, were seen as highly correlated with an alarming degree of risk of death (16).

We were able to highlight the increased mean platelet volume (MPV) and platelet hyperactivity that we often found in COVID-19 patients with a reduced level in overall platelet count since erythroid and myeloid lineage progenitors appear to be the only cell types expressing both ACE2 and TMPRSS2 among the cells present in the bone marrow (16, 17, 19-22).

Events that ultimately demonstrated the contamination of the erythroid lineage by the virus during the differentiation phase and the reduced number of platelets due to the autoimmune attack by T cells, neutrophils, and NK cells (17, 19-22) (Fig. 4). The panel of cytokines considered also revealed an association with hospitalization time, age and sex.

The typical COVID-19 patient

anosmia, ageusia, light fever, light headache and dry cough, deep fatigue;
marked alkalotic, hypoxic, hypocapnia, the ABG profile with hyperventilation at the time of admission;
the laboratory and microbiology results showed lymphopenia, neutrophilia;
fibrinogen, ESR, CRP, vitamin D and eGFR were markedly anomalous;
markedly high IL-6 levels;
thrombocytopenia, anemia;
BALF showed the presence of few opportunistic pathogens Klebsiella spp, Candida albicans, Aspergillus, Pseudomonas spp.
Total number of CD4+ and CD8+ T cells showed a drastic decrease in COVID-19 patients with levels lower than the normal range delimited by 400/uL and 800/uL, respectively, and were negatively correlated with blood inflammatory responses;
low level of B lymphocytes, low level of T-reg CD4+CD25+high and high level of T killer cells, high level of CD8+CD57+ suppressor, high level of CD8+ CD38+DR+, and monocytes were seen in COVID-19 patients.
Patient with mild to severe COVID-19 infection revealed the carry a precise genetic make-up of SNPs related to those genes regulating the immune responses

Fig. 4. *The overall picture of affected patients was a result that we reached gradually based on the clinical, laboratory, and investigative approaches.*

Patient-associated cytokine signatures were partially and included molecules that have been implicated in the pathogenesis of COVID-19, such as IL-6, eGFR, vitamin D3, and fibrinogen, as well as molecules that are more generally associated with inflammation/infection, such as ESR, D-dimer, CRP and iron (23).

Thus, the cell-mediated immune response significantly increases in COVID-19 cases compared to other patients. In this case, we assumed the necessary existence of a lung-kidney-heart cross-talk; this simultaneously explains the whole complexity of COVID-19 disease and its mechanism of progression along with uncontrolled autoimmune responses under the guidance of IL-6 leading to the well-known “cytokine storm” (1-5, 12, 13, 15, 16).

The data obtained from our analysis aligned with the results of observational studies, which confirmed that a reduced vitamin D level, in a concentration lower than 20 ng/mL, was a distinctive feature in COVID-19 patients and was related to a poor prognosis (19).

Regarding our main clinical findings, a clear reduction of platelets and erythrocytes was observed, an event related to the deficit found in the immune system response towards its own affected cells infected by SARS-CoV-2. Initially, all the focus was on containing the spread of autoimmune reactions and uncontrolled inflammatory flare-ups, providing a therapy based on both anti-inflammatories, antioxidants, and two types of antibiotics to stop a secondary type of bacterial infection often associated with COVID-19 to meet the increasing need for lost immune modulation as a consequent reduction of the lack of immunoregulatory cells and cytokines (3, 4, 7, 9-11).

The results showed profoundly compromised immune system during SARS-CoV-2 infection, lymphopenia (64%), low level of B lymphocytes (60%), low level of CD4+CD25+high T-reg (37.8%) and high level of killer T cells

(73.3%), high level of CD8+CD57+ suppressor (64.44%), high level of CD8+CD38+DR+ (80%) and monocytes (28.9%) were obvious features observed in COVID-19 patients (15). As lung capacity begins to decay due to the lack of microvascular homeostasis, cardiovascular functions also worsen, affecting the reuptake of filtered 25-hydroxyvitamin D in renal proximal tubules (20, 21, 23).

Vitamin D has endocrine, paracrine and autocrine functions. RAS is inhibited by vitamin D due to its involvement in preventing angiotensin II (Ang-II) accumulation via inhibition of renin release, a very common event in COVID-19 patients (23, 24). Increased Ang-II in cholesterol plaque accumulation along arteries, veins and visceral glomerular epithelial cells (podocytes) is a well-known phenomenon that induces cholesterol metabolism dysfunction leading to renal and cardiovascular injury (23). In this scenario, we then considered the increased toxic effects of the spike protein, which is known to promote Ang II accumulation, explaining cardiac hypertrophy and heart failure. Indeed, Ang-II is produced within the myocardium; Ang-II is activated within the hypertrophic heart in myocardial failure; pharmacological inhibition of RAS and Ang-II in animal models and in patients with hypertrophic hearts presenting with myocardial failure have shown to be highly effective (25-28).

The great disparity of individuals affected by COVID-19 contributed to confusing the scene. Exposure to the virus could not explain the variety of responses to the virus and the profound differences between those who showed the disease and those who, on the contrary, did not show it, despite their direct contact with the infected.

The pre-infection health status and the state of immune defenses were soon confirmed as key players in the progression of the disease. However, there was a need to explain the genetic composition of the hosts concerning susceptibility and risk of COVID-19 (22, 23).

The results of genetic tests performed on patients highlighted that the genetic composition of the host was shown to exert a direct influence on the degree of predisposition and outcomes of COVID-19. One of the best results in this direction was to investigate and highlight the presence of single nucleotide polymorphisms (SNPs) of those genes involved in the immune regulation mechanism. In fact, the degree of severity of the disease was soon observed in relation to the presence of specific SNPs (21).

The overall results showed the following: ACE-1 (higher prevalence of I/D in the COVID-19 group), Serpina3 (higher prevalence of G/T in the COVID-19 group), CRP (higher prevalence of G/G in the healthy group), IL6 rs1800795 (higher prevalence of G/G-G/C in the COVID-19 group) and IL10 (higher prevalence of G/A in the healthy group; higher prevalence of A/A in the COVID-19 group) and IL1RN (higher prevalence of C/T-T/T in the COVID-19 group; higher prevalence of C/C in the healthy group), IL6R (lower prevalence of A/A in the COVID-19 group), VDR (higher prevalence of Fok1 TC in the COVID-19 group and higher prevalence of T/T in the healthy group; higher prevalence of Taq1 A/G in the COVID-19 group, higher prevalence of G/G in the healthy group). healthy group), IFNγ (lower prevalence of A/A in the COVID-19 group), A/T higher prevalence in the healthy group), and TNFα (G/G higher prevalence in the COVID-19 group) (Fig. 3) (21, 22).

Final consideration and the problem of the "Long COVID"

One of the lessons of the COVID pandemic is the importance of multidisciplinarity to achieve effective diagnosis, treatment, and prevention (28-30). Cooperation between primary emergency care and secondary care is indispensable; thus, cooperation between different departments and disciplines, such as emergency medicine, immunology, and microbiology departments (31-33).

Many COVID-19 patients had comorbidities at the time of admission, but many others reported long-term effects of the infection, later called long COVID syndrome. These patients showed a very particular clinical picture and were often severely ill. Management of patients with comorbidities and long COVID requires a multidisciplinary approach and treatment to achieve complete recovery.

Recently, some symptoms have been described in patients a few months after being affected by COVID-19. In the literature, many symptoms recur and vary from foggy thoughts, anemia, neuromyasthenia, vegetative neuritis, post-viral fatigue syndrome, sleep disturbances, raphe nucleus encephalopathy, chronic lung conditions (pulmonary interstitial fibrotic scarring) and chronic mononucleosis syndrome among others (34, 35).

This virus (RNA-virus) and the vaccines (mRNA) that are analogous can start with uncontrolled immune responses that lead to extreme "central" decay, a picture that also includes a reduction in B lymphocytes, an increase in pro-inflammatory cytokines (IL-6, IL8, TNFα), an increase in glial macrophages (M1) (responsible neural inflammation) and activation of autoreactive T cells (cytotoxic T cells and Th1) (34, 35).

From these results, we assume that the post-COVID condition will surely represent another challenge for healthcare professionals since these signs should also refer to pre-existing comorbidities that are deeply linked to a higher correlated burden.

This varied symptomatic picture indicates a common Long-COVID condition, suggesting that the SARS-CoV-2 variants may be connected. We suggest that the pathogenic spike protein of SARS-CoV-2 and the cell-cell mechanisms associated with the Long-COVID syndrome may be similar but not the same among the different SARS-CoV-2 variants (34).

The data and overall outcomes would support this hypothesis: individuals affected by the early variants showed a higher number of post-COVID symptoms, especially respiratory symptoms such as dyspnea, fever, and fatigue, compared to patients infected by the later variants. Many showed lung fibrotic tissues validated by chest CT even after 12 months of COVID-19 infection (36, 37). However, exposure to infection alone failed to support the great variety of each individual's responses to the virus and the huge diversity of signs and symptoms (22).

Consequently, it is expected that the development of infection and post-infection symptoms will be higher not only in the presence of historical variants and pre-existing conditions but also with mRNA vaccines. All of this is influenced by a predisposing genetic environment (22, 23, 36-38). Proposing innovative, albeit complex, research strategies and clinical procedures to address and solve the abovementioned problems has not been easy. However, despite the difficulties, 118 SET demonstrated that this approach was effective in reducing mortality and generating a new effective and deliberate discussion on the COVID-19 pandemic by stimulating new perspectives and concrete actions on future plans, priorities, and strategies (36-39).

The proposed emergency plan algorithm helped keep everyone involved and raise awareness and questions, allowing concrete goals to be achieved step by step for various health problems. Our health services' complex challenges were enormous and could not be achieved without multidisciplinary exchanges and debates.

Teamwork was of great help in standardizing health procedures and improving network governance in the province of Taranto, strengthening the impact of health services on population health, which in the post-COVID era is more necessary than ever. So, with this article, we proposed a new procedure that could become a "Know-how" tool for the formation of well-organized interdisciplinary teams of health professionals. The effectiveness of this procedure during the pandemic has been tested. Hence, we sincerely hope that it will be used in the future to help healthcare professionals solve the next new global challenges.

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