


Boosting ICU capacity during the COVID-19 pandemic in the western Balkan region, The Republic of Srpska experience

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Abstract

Background: Response to the outbreak of poliomyelitis in mid-1950 led to recognition and consequent development of critical care. Seventy years later the humankind was struck by COVID-19, another major challenge for critical care medicine which was especially big in Low-Resources-Settings where more than two thirds of the world population live, including the population of the Republic of Srpska (RS).

Design and methods: The main aim was to show an overview of all interventions in order to boost hospitals' capacities to the level which is sufficient to manage high amount of critically ill COVID-19 patients in the RS. A before-after cohort study design was conducted to evaluate the effects of interventions for increase in preparedness and capacity of ICUs for admission and treatment of COVID-19 critically ill patients in nine hospitals in the RS. Results: Following interventions, the biggest and university affiliated hospital in the RS has increased ICU capacities: total number of ICU beds increased by 38% and number of ventilators by 114%. Availability of machines for veno-venous extracorporeal membrane oxygenation (vvECMO) increased by 100%. Number of doctors who were involved in treatment of critically ill patients increased by 47% and nurse/patient's ratio reached 1:2.5. Similarly, all other hospitals experienced boosting of ICU beds by 189% and ventilators by 373% while number of doctors increased by 108% and nurse/patient's ratio reached 1:4.

Conclusion: All interventions implemented during COVID-19 pandemic outbreak in the RS resulted in increasing capacity for treatment of critically ill patients, but the education of health care professionals was identified as the most important conducted intervention.

Keywords

Critical care medicine, capacity boosting, low resources settings

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Introduction

Basic information

Coronavirus disease 2019 (COVID-19) is a new infectious disease which affects respiratory system. It was first reported in China (Wuhan) and it has subsequently spread worldwide affecting almost every healthcare system globally with tremendous impact on global health, especially in low resources settings (LRS).^{1,2} Reports during the initial phase of the pandemic suggest that among those with COVID-19, up to 20% develop severe disease requiring hospitalization. Among those who are hospitalized, up to one-quarter need intensive care unit (ICU) admission, representing approximately 5%–8% of the total infected population.^{3–8} At the very beginning of COVID-19 pandemic, healthcare workers, stressed by large numbers of patients, insufficient supplies (ventilators and other ICU machines) and experiencing infection control concerns, have struggled to extract useful information from different valid sources into practical recommendations that can be readily implemented at the bedside. These challenges have been even more formidable in LRS.^{9,10}

Critical care medicine in LRS, what have we learned so far?

Generally, the burden of critical illness in LRS is substantial and mortality rates remain unacceptably high when compared to high income countries (HIC). In pandemic period, the problem of mortality rates is probably even bigger in these settings. The main causes of poor outcome of critical illness are limited capacity for nonsurgical critically ill patients, small number of medical intensive care units (MICUs), insufficient number of ICU beds, lack of trained staff and poor academic and research resources in LRS. It is estimated that the number of ICU beds in low- and middle-income countries (LMICs) is 0.1–2.5 per 100,000 population. In contrast, HIC have as many as 30 ICU beds per 100,000 population. While data on structure, treatment and outcomes in LRS (LMICs) are scarce, data from HIC cannot be easily extrapolated.^{2,10,11}

Health care challenges in the Republic of Srpska (Bosnia and Herzegovina)

Bosnia and Herzegovina (B&H) is one of countries that emerged after the dissolution of the Yugoslavia.¹² As a result of the Dayton Peace Agreement, today's Bosnia and Herzegovina consists of two parts, the Republic of Srpska and the Federation of Bosnia and Herzegovina. B&H is located in South Eastern Europe (West Balkan region). In its recent history, it has endured 4 years of war, international isolation (sanctions imposed by the international community) and severe social and economic devastation, including numerous refugees and displaced persons. Each

of these events has left a deep scar in the Republic of Srpska's (B&H's) healthcare system, including critical care medicine.^{11–13} Currently, the World Bank classifies B&H (as well as RS) as an upper-middle income country,¹⁴ but its health care system and problems related to the treatment of critically ill patients are quite similar to LMICs and accordingly it can be defined as a LRS. When we talk or write about low resources countries, we have to be aware that these countries are not situated somewhere in Africa, but in the heart of Europe (the Western Balkan where is Bosnia and Herzegovina situated). The definition of LRS is used throughout this article to refer to health care systems in LMICs (as well as upper middle-income countries), acknowledging that LRS exist even in HICs.¹⁵ On the other hand, provision of critical care services in LRS are challenged with its high costs, insufficient numbers of ICU beds, lack of trained staff (doctors and nurses) and with insufficient academic and research resources.^{2,10,11} Before the COVID-19 outbreak, education of undergraduate medical students and residents in non-surgical branches (internal medicine, cardiology, neurology, and infectology) did not include obligatory rotation (or any theoretical knowledge) in the intensive care units. In the Republic of Srpska only pulmonology residents have critical care training and obligatory 6 months rotation in ICU. This was defined at the beginning of 2015 as a result of suggestion of pulmonologists from the MICU of UCC RS. Nine (9) hospitals operate in the Republic of Srpska; the biggest one and university affiliated, is the Clinical Centre of the Republic of Srpska, while other ones are general hospitals. One general hospital (Foča) is teaching hospital and serves as a teaching basis for Medical school of the University of East Sarajevo (Figure 1).

Establishment of the very first modern Medical ICU in the Republic of Srpska (B&H)

Key authorities of UCC RS and Ministry of Health of the Republic of Srpska started the project of establishing the first modern MICU at UCC RS Banja Luka. The MICU started operating at the end of 2008.¹⁶ Over the next 14 years MICU has moved to the newly built north wing of UCC RS with staff expansion to 21 physicians (10 critical care specialists) and 60 nurses. The primary specialties of this multidisciplinary team include pulmonology (10 physicians), internal medicine (9 physicians), anesthesiology (1 physician), neurology (1 physician), and infectious diseases (1 physician). The new space and equipment (2019) allow admission and treatment of up to 28 critically ill patients, with provision of full support to all organ systems. At present, this MICU is the only level three and ISO 9001: 2015 certified MICU in the Republic of Srpska (and in B&H as well). MICU at UCC RS was defined as a referral center for treatment of critically ill patients for the region of the Republic of Srpska (approximately 1,000,000 inhabitants).¹⁰

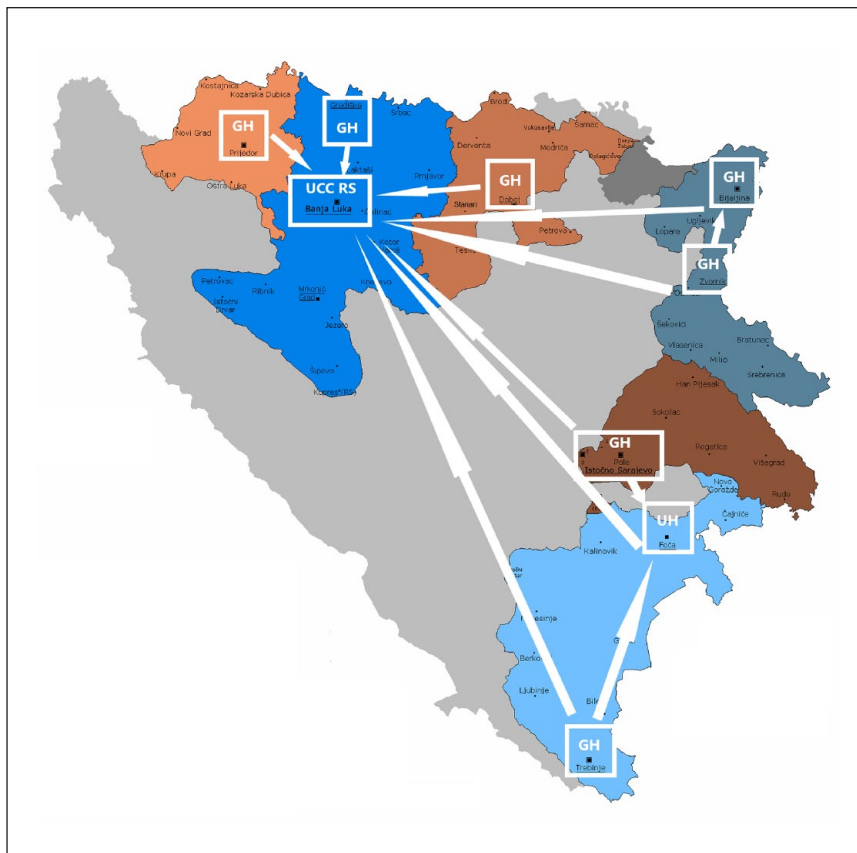


Figure 1. Geographical distribution of all hospitals in The Republic of Srpska and paths of critically ill patients' referrals. UCC RS: University Clinical Centre of the Republic of Srpska; GH: general hospital; UH: University hospital.

Since the establishment of the MICU in Banja Luka, critically ill patients from the whole Republic of Srpska are being transferred to UCC RS's MICU (Figure 1).

It is very important to notice that although no objective data from low resources settings are readily accessible, investigators from these countries are often under-represented in international non-governmental organizations responding to emergencies such as the present pandemic. The presumed inability of health care workers and researchers from LRS to implement improvement interventions and participate in observational and interventional research, creates a vicious cycle leading to lack of data, impractical guidelines and irrelevant research projects.

Because of everything mentioned above, a study was created with the aims to provide an overview of all activities (interventions) in order to capacitate (boost) hospitals to manage high amount of critically ill COVID-19 patients in the Republic of Srpska (LRS model country).

Methods

Study setting

The study was conducted in the Republic of Srpska, which health and educational systems are separately organized

from the Federation of Bosnia and Herzegovina. The Republic of Srpska provides universal public health insurance to its inhabitants. Since the beginning of the pandemic, all COVID-19 patients have had full access to free healthcare, regardless of the basic pre-pandemic insurance status.

Study design and the analysis

Using a before-after cohort study design, the investigators evaluated the effects of interventions on the capacity building (boost) and preparedness increase of ICUs for admission and treatment of COVID-19 critically ill patients in nine hospitals in the Republic of Srpska. The survey recorded the following data: type of hospital, number of ICU beds, number of ventilators, nurse-to-patient ratio, number of intensivists, anesthesiologists, infectious disease specialists, pulmonary specialists, residents, and critical care fellows at the beginning of 2020 and at the beginning of 2022. Additionally, a survey was conducted among all doctors and main nurses who worked in these ICUs to evaluate the availability of basic and advanced critical care training programs (official and unofficial). The main source of data was the Ministry of Health and

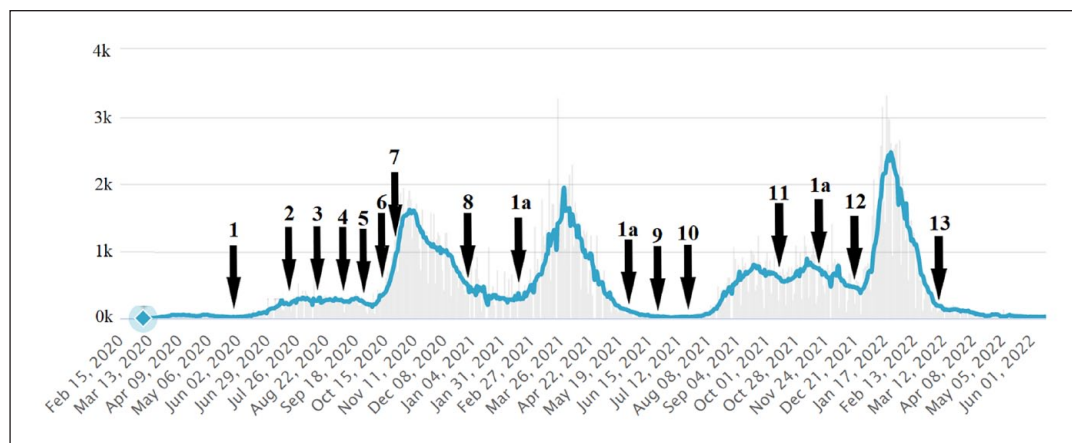


Figure 2. Timeline of interventions performed to health care system of the Republic of Srpska in relation to pandemic waves. 1—Equipment purchase (ICU ventilators) 2—reorganization and construction works in UCC RS, 3—visiting the intensivists from MICU UCC RS to other hospitals in RS with an aim to evaluate organization of their ICU services, 4—beginning of reconstruction in order to create new ICUs for the treatment of COVID 19 critically ill patients, 5—starting the unofficial critical care training of doctors and nurses by critical care experts from MICU UCC RS, 6—start of the WHO support in unofficial critical care training for health care workers in the Republic of Srpska, 7—start of the very first critical care education for undergraduate medical students at the Medical School in Foca (University East Sarajevo), 8—implementation of Fundamental Critical Care Support Course in MICU UCC RS for doctors from all hospitals of the Republic of Srpska, 1a—continued procurement of equipment, 9—creation of new department for treatment of COVID-19 critically ill patients, named NIV center, 10—implementation of the intensive care teaching curricula for medical students (Medical School in Foca), 11—adaptation of the curricula for all specializations in the field of non-surgical medicine branches (Medical schools in Banja Luka and Foca), 12—establishment of critical care department at the Medical School University of Banja Luka, 13—the very first textbook named: “Basics of critical care” published (Publisher: Medical School University of Banja Luka).

Social Welfare in the Republic of Srpska government. All data were recorded at the beginning of April 2022.

Interventions

Interventions were conducted by governmental and non-governmental organizations (NGOs), between May 2020 and April 2022. Governmental organizations which were involved in interventions were Ministry of health and social welfare of the Republic of Srpska, Health Insurance Fund of the Republic of Srpska, University Clinical Centre of Republic of Srpska (as the referral and biggest medical center), and Medical Faculties of Universities of Banja Luka and East Sarajevo. From the group of non-governmental organizations, interventions were supported by national society of intensivists named Medical intensive care society, World Health Organization (WHO), and Society of critical care medicine (SCCM). Intervention was conducted in several phases:

Phase 1—Purchase of equipment (ventilators, patient monitors, suction pumps, and infusion pumps). This intervention was realized by governmental organizations, mainly Health Insurance Fund of the Republic of Srpska and Ministry of health and social welfare of the Republic of Srpska.

Phase 2—Construction works in hospitals in order to increase the capacity to treat critically ill. These

interventions were performed directly in cooperation of hospitals with Ministry of health and social welfare of the Republic of Srpska.

Phase 3—Education of health care workers (physicians and nurses) from the field of critical care. This intervention was carried out both by governmental and non-governmental organizations. Continuing medical education in our country is available in two forms, as official training within the form of specialization and subspecialization (fellowship), and as unofficial training in the form of courses or workshops. All forms of education are conducted at the bedside or via a video link. The two governmental organizations that provide official and unofficial training (education) are Ministry of health and social welfare of the Republic of Srpska and Medical faculties of Universities of Banja Luka and East Sarajevo. NGOs that took part in the process of unofficial education in the Republic of Srpska were: Medical intensive care society, WHO office in Sarajevo and SCCM (USA). All educational activities that required physical presence of physicians (at bedside) were organized and conducted exclusively at the Medical Intensive Care Unit (MICU) of the University Clinical Centre of Republic of Srpska—currently the most advanced multidisciplinary MICU in Bosnia and Herzegovina (level 3 ICU) with 10 officially trained intensivist and 3 professors from the field of critical care (Figure 2).

Results

University Clinical Centre of the Republic of Srpska (UCC RS)

Banja Luka, the capital of the Republic of Srpska has approximately 200,000 inhabitants. The University Clinical Centre of the Republic of Srpska is situated in Banja Luka and has 1198 hospital beds. At the beginning of 2020 there were five types of ICUs in the UCC RS (MICU, SICU, Pediatric ICU, Neonatal ICU, and Gynecological ICU) with 78 ICU beds and 58 ventilators. However, at the beginning of April 2022, UCC RS has six types of ICUs with 108 ICU beds and 124 modern ICU ventilators. Additional ICU was affiliated to MICU with a purpose of treating patients using non-invasive ventilation and high flow oxygen therapy (HFNC). Total number of ICU beds increased by 38% and ventilators by 114%. In these period, number of machines for veno-venous extracorporeal membrane oxygenation (vvECMO) increased

by 100% (Table 1). At the beginning of 2020 treatment of critically ill patients in the UCC RS was performed in MICU and SICU (anesthesiology department). Number of doctors (residents, specialists, fellows, and subspecialists) who were involved in treatment of critically ill patients till the beginning of April 2022 increased by 47% (Table 2.) Nurse/patients ratio in ICUs of UCC RS was 1:4 at the beginning of 2020, however this ratio changed to 1:2.5 during 2 years of COVID pandemic.

Other general hospitals in the Republic of Srpska

In other eight (8) general hospitals just one type of ICU (SICU or mixed ICU) existed at the beginning of COVID-19 outbreak. Number of ICU beds at the beginning of the studied period in all general hospitals was 66 and it increased by 189% during 2 years (191). All hospitals had 41 ventilators in total at their disposal at the beginning of

Table 1. Data on population distribution in the Republic of Srpska and comparison of hospitals' capacities between years 2020 and 2022.

Cities in the Republic of Srpska	Number of inhabitants	Type of hospital	Total number of beds	Type of ICU in January 2020	Type of ICU in January 2022	Number of ICU beds in January 2020/2022	Number of ICU ventilators in January 2020/2022	Number of ECMO machines in January 2020/2022
Banja Luka	≈200,000	Tertiary—University affiliated Clinical Center	1198	1) Medical ICU 2) Surgical 3) Recovery 4) Gynecological 5) Pediatric	1) Medical ICU 1a) NIV center 2) Surgical 3) Recovery 4) Gynecological 5) Pediatric	28/28 0/26 20/20 14/18 8/8 8/8	22/30 0/28 18/26 2/20 8/10 8/10	MICU—2/4
Gradiska	≈67,000	General	200	1) Surgical/mix ICU	1) Surgical ICU/mix ICU 2) COVID ICU	9/5 0/10	5/7 0/14	-
Prijedor	≈100,000	General	367	1) Surgical/mix ICU	1) Surgical ICU/mix ICU 2) COVID ICU	10/10 0/14	3/10 0/14	-
Doboj	≈80,000	General	522	1) Surgical/mix ICU	1) Surgical ICU 2) COVID ICU/ MICU	5/6 0/14	5/6 0/16	-
Bijeljina	≈120,000	General	239	1) Surgical/mix ICU	1) Surgical ICU// mix ICU 2) COVID ICU	10/10 0/40	10/10 0/30	-
Zvornik	≈64,000	General	210	1) Surgical/mix ICU	1) Surgical ICU// mix ICU 2) COVID HDU/ MHU	7/7 0/16	5/6 0/20	-
Foca	≈10,000	Secondary—Teaching hospital	230	1) Surgical/mix ICU	1) Surgical ICU// mix ICU 2) COVID ICU/ MICU	6/6 0/10	5/8 0/13	-
East Sarajevo	≈61,000	General	180	1) Surgical/mix ICU	1) Mix ICU 2) COVID ICU	13/13 0/13	4/4 0/21	-
Trebinje	≈32,000	General	168	1) Surgical/mix ICU	1) Surgical ICU// mix ICU 2) COVID ICU	6/6 0/11	4/4 0/11	-

Table 2. Data on change in structure of critical care physicians in hospitals in 2022 compared to 2020.

Cities in the Republic of Srpska	Type of hospital	Number of critical care physicians January 2020/2022
Banja Luka	Tertiary—University affiliated Clinical Center (University Clinical Centre of the Republic of Srpska)	MICU: Intensivists—5/7 On fellowship—5/3 Specialists—7/10 Residents—8/12 AD: Specialists—30/32 Residents—20/22 PD: Specialists—0/2 Residents—2/10 CD: Specialists—0/0 Residents—0/10 ID: Specialists—0/0 Residents—0/5
Gradiska	General	SICU/MixICU/COVID: On fellowship—1/0 Intensivist—0/1 (anesthesiologist) Specialists—3/3 (anesthesiologists) Residents—0/3 (anesthesiology)
Prijedor	General	SICU/MixICU/COVID: Specialists—5/5 (anesthesiologist) Residents—0/1 (anesthesiology)
Doboj	General	SICU: On fellowship—0/1 (anesthesiologist) Specialists—7/7 (anesthesiologist) Residents—2/2 COVID/MICU: On Fellowship—0/2 (Anesthesiologist—1; pulmonologist—1) Specialists—0/2 (Anesthesiologist—1; pulmonologist—1) Residents—0/3 (Anesthesiology—1, pulmonology—1, internal medicine—3)
Bijeljina	General	SICU/MixICU/COVID: Specialists—7/12 (anesthesiologists) Residents—4/8 (Anesthesiology—4, pulmonology—1, internal medicine—1, and surgery—2)
Zvornik	General	SICU/MixICU: Specialists—3/3 (anesthesiologists) Residents—2/5 (anesthesiology) COVID/HDU: Specialists—0/6 (internal medicine—5 and cardiologist—1) Residents—0/4 (internal medicine—1, infectology—1, and anesthesiology—2)
Foca	Secondary—Teaching hospital	SICU: Specialists—7/ 6 (anesthesiologists) Residents—0/4 (anesthesiology) COVID/MICU: On fellowship—0/1 (infectologist) Specialist—0/5 (anesthesiologist) Residents—0/2 (internal medicine)
East Sarajevo	General	SICU/MixICU/COVID: Specialists—3/ 5 (anesthesiologists) Residents—0/4
Trebinje	General	SICU/MixICU/COVID: On Fellowship—0/1 (anesthesiologist) Specialists—3/3 (anesthesiologists) Residents—2/3

2020 and after intervention of governmental institutions this number increased by 373% (194; Table 1). Number of critical care physicians at the beginning of 2020 was 49 (mostly anesthesiologist) and it increased by 108% in 2-year time (102; Table 2). Nurse/patient ratio in ICUs in general hospitals in the Republic of Srpska was 1:6 at the beginning of 2020, however this ratio changed to 1:4 during 2 years of COVID-19 pandemic.

Discussion

The main finding of this study shows that acquisition of medical equipment, performing additional construction works in hospital wards and establishment of new ICUs are goals easier to achieve (even in pandemic and emergencies situations) than creating well educated critical care professionals. The impact of previously established modern multidisciplinary MICU in the Republic of Srpska to all described interventions was tremendous. All activities (interventions) conducted throughout the Republic of Srpska which led to increase of capacities for the treatment of critically ill COVID-19 were coordinated by experts from MICU at UCC RS. Support by medical experts (intensivists) was equally provided to governmental and non-governmental organizations. Literature source (data) of similar experiences in the Western Balkan countries are scarce and knowledge is limited (especially in LMICs and in low resource settings generally). Due to many differences in health care systems, a regional (area of Balkans—South-East Europe) analysis may be helpful. To the best of our knowledge, our study is the only one conducted in the area of Balkans that determines interventions conducted with an aim to increase capacities for treatment of COVID-19 critically ill patients during pandemic. All described interventions are mostly performed in COVID-19 free periods (in-between pandemic waves).

Interventions performed in the health care system of the Republic of Srpska

Immediately after the outbreak of the COVID-19 pandemic in the world, the health care authorities in the Republic of Srpska realized that the capacities for the treatment of the critically ill patients are insufficient. The first intervention was purchasing medical equipment, mostly ICU ventilators. Governmental institutions finalized the purchase of equipment and delivery of all ventilators throughout the Republic of Srpska started at the beginning of Jun 2020. This intervention was a great success for governmental institutions because the Republic of Srpska is very small market and in the chaotic first months of the pandemic COVID-19 the procurement of ICU ventilators was extremely difficult.^{17–19} Group of experts from the field of critical care (MICU at UCC RS) visited all general hospitals in the Republic of Srpska during the

summer of 2020, when the number of COVID-19 patients temporarily decreased. Main aim of this exploration (visiting and screening) was to identify problems but also the opportunities for the implementation of critical care and establishment of the new ICUs. Shortly after providing suggestions by the experts, almost all hospitals in the health care system of the Republic of Srpska started construction works with main aim to establish new ICU departments especially for the treatment of COVID-19 critically ill patients. Main aim of construction works in the UCC RS was to increase oxygen supplies throughout the hospital pipelines to supply increasing number of ICU ventilators. In addition to oxygen, a pipeline was made for the supply of compressed air. After this intervention Pulmonary Department (PD) was capable to treat 26 critically ill patients using ICU ventilators. Similar expert recommendations followed by construction activities were performed worldwide.^{20–23}

Procurement of equipment and reconstruction of hospital walls were done relatively fast, whereupon health care authorities recognized a much bigger and more significant problem—the lack of trained staff.²⁴ At the very beginning of the pandemic crisis WHO identified education as a major priority especially in LRS, but distance and resources remained significant barriers to rapid education dissemination.²⁵ In the pre-pandemic period treatment of critically ill patients was conducted by intensivist (subspecialists) only in the MICU UCC RS. In the rest of the Republic of Srpska, care of these patients was provided only by anesthesiologists. This was very similar to other low resources countries.²⁶ Dominant intervention in observed, 2-year period, in the Republic of Srpska was education. In the beginning, unofficial type of education from the field of critical care was used mainly in the forms of certified courses (e.g. Fundamental Critical Care Support Course) and continuous medical education (CME). Official education in the form of specialization and critical care fellowship began exactly 1 year after the COVID-19 outbreak. Both types of education were recognized and supported by governmental institutions (Medical School University of Banja Luka and Ministry of Health and Welfare of the Republic of Srpska) and NGOs (The National society of critical care, WHO, and SCCM). The impact of the 2 years interventions on educational system is positive in the long run: (a) curriculum for undergraduate medical students has been changed and intensive medicine became obligatory course (subject) in the final year of studies for all Medical Schools in the Republic of Srpska, (b) curriculum for residents of non-surgical branches (internal medicine, pulmonology, cardiology, infective diseases, and neurology) was changed and practical and theoretical critical care training became obligatory; all residents in the Republic of Srpska have to spend 3–6 months at the MICU, (c) for the very first-time textbook “Basics of critical care” was published by Medical School University of Banja Luka and by the National society of

critical care, (d) in two hospitals (GH Doboj and UH Foča) COVID-19 ICU was converted to MICU with multidisciplinary team of physicians, (e) five doctors (from GH Doboj, GH, Trebinje, and UH Foča) started critical care fellowship at the MICU (UCC RS), (f) Health care authorities in the Republic of Srpska decided to build completely new hospitals (UH Doboj and UH Trebinje) with two types of ICU, surgical and medical, increasing the number of ICU beds, (g) recognized and partially resolved problem of transportation of critically ill patients from general hospitals to UCC RS, (h) recognized and partially resolved problem of delayed recognition of critically ill COVID-19 patients treated at the emergency departments and regular wards. Similar programs of educations (FCCS), redeployment and involvement of residents in the treatment critically ill COVID-19 patients were performed in other settings.²⁷⁻²⁹

Limitations and the strength

The most important limitation of the study can be found in the fact that it was a single-country (single-republic) design. The lack of data regarding the outcome of the treatment of critically ill patients in the Republic of Srpska after the intervention represents a significant limitation. Additionally, presence of negligible number of scientific research in low-resources countries and lack of reporting about response (interventions) to the COVID-19 pandemic in these settings might be seen as invisible limitations. This type of research sometimes can be accompanied by political and public impact, hence response outcomes in these countries are often much worse, compared to HICs. Main strength of this study is that it showed the outcomes of the interventions implemented the Republic of Srpska (typical represent of Western Balkan) with the main aim to increase ICU capacities. Any study published in low resources countries and LMICs can stimulate other researchers from these settings to publish their results, this is invisible strength as well.

Conclusion

In conclusion, all interventions implemented during COVID-19 pandemic outbreak in the Republic of Srpska resulted in increased capacity for treatment of critically ill patients. Procurement of equipment and reconstruction of hospital walls were done relatively fast, (approximately in several months), but education of doctors and nurses took a longer period of time. Organization of educational activities performed during pandemic was the most difficult intervention to implement and initially included unofficial education (workshop courses), and then official education (specialization and fellowship). All these interventions resulted in rapid development of critical care medicine as a medical branch generally, but we identified education of health care professionals as the most important conducted

intervention with long term effects on health care and educational systems of the Republic of Srpska. Existence of modern multidisciplinary MICU in pre-pandemic period accelerated all described processes. The interventions assessed in this study offers an excellent model for increasing capacity for treatment of critically ill patients generally and can be especially valuable to low resources settings where critical care expertise is lacking.

Author contributions

SD participated in the analysis and interpretation of the data and drafted the manuscript. DM, BZ, MJ, TK, DB, ML, and AS participated in the collection of the data and revised the manuscript. VDj and RS participated in the design of the study and coordination. PK had primary responsibility for study design, data analysis, interpretation of data, and writing the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Availability of data and materials

The datasets used and/or analyzed in the present study are available from the corresponding author on reasonable request.

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