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Convalescent anti-SARS-CoV-2 plasma for the treatment of patients with COVID-19: a retrospective study RESCOVID-19

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Abstract

Purpose Convalescent plasma (CP) collected from people who recovered from COVID-19 became a rapidly available treatment modality in numerous countries, including the Czech Republic. The aims of our study were to evaluate the effectiveness and safety of CP in the treatment of COVID-19.

Methods This retrospective observational study involved six Czech hospitals. This study enrolled patients with and without CP treatment who were hospitalized between April 2020 and April 2021. Propensity score matching and logistic regression analysis were performed to evaluate the influence of CP administration and its timing on the in-hospital survival of COVID-19 patients.

Results A total of 1,498 patients were enrolled in the study; 406 (27%) were administered CP, and 1,092 (73%) were not treated with CP. The propensity score-matched control group consisted of 1,218 subjects. The survival of patients treated with CP was 79%, while that of patients in the matched control group was 62% ($P<0.001$). Moreover, the chance of survival was significantly greater when CP was administered within three days after the onset of COVID-19 symptoms than when CP was administered after four or more days (87% vs. 76%, $P<0.001$). In addition, adverse effects related to CP administration were recorded in only 2% of patients and were considered mild in all patients.

Conclusions Our study demonstrated that the administration of CP was safe and possibly associated with positive effects that were more pronounced if CP was administered within the first three days after the onset of COVID-19 symptoms.

Keywords COVID-19, SARS-CoV-2, Convalescent plasma, Outcome

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Introduction

Convalescent plasma (CP) obtained from people who recovered from a SARS-CoV-2 infection became a promising treatment option at the beginning of the COVID-19 pandemic. The main aim of this treatment is specific passive immunization with anti-SARS-CoV-2 neutralizing antibodies. At the same time, CP may have other immune mechanisms, such as enhancement of antibody-induced cellular cytotoxicity, an improvement of phagocytosis, and blocking the entry of the virus into target cells [1–6]. Plasma collected from patients recovering from infectious diseases has been used in the past for the prophylaxis and/or treatment of several infectious diseases [7, 8]. The first large-scale use of CP during the Spanish flu (H1N1) pandemic in 1918–1920 indicated that the use of CP was associated with a significant reduction in mortality [9]. Prior to the SARS-CoV-2 pandemic, CP was routinely used to treat Argentine hemorrhagic fever. Moreover, there have been attempts to treat Ebola virus disease, avian and pandemic H1N1 influenza, as well as coronavirus infections SARS and MERS [10–12]. In several countries, national programs were initiated for the production and use of CP for the treatment of COVID-19 patients [13, 14]. The European Union supported the production of CP in its continuously updated recommendations [15]. On the other hand, the effectiveness of CP for the treatment of COVID-19 patients has not been confirmed despite a growing number of studies evaluating the use of CP [16–18]. Thus, the lack of robust and unequivocal evidence for the efficacy of CP, together with the advent of SARS-CoV-2-specific monoclonal antibodies and the first approved antiviral drug, led to the termination of CP use during the first half of 2021.

In the Czech Republic, the production of anti-SARS-CoV-2 CP started in April 2020. During the period from April 2020 to April 2021, CP was administered to 5.4% of the 131,000 patients with COVID-19 who were hospitalized in the given period [19]. This represents a large cohort of COVID-19 patients, enabling a retrospective analysis of CP efficacy.

Thus, the main objective of the current study was to evaluate the influence of CP on the survival of COVID-19 patients in a propensity score-matched analysis. The secondary aims were to determine the best treatment timing and to determine the safety of CP administration.

Methods

Study population and design

This retrospective observational study enrolled COVID-19 patients hospitalized from the 1st of March 2020 until the 1st of March 2021 (12 months). This period was characterized by changing frequencies of dominant SARS-CoV-2 lineages, beginning with lineage B.1 in the spring of 2020, which was displaced by lineage B.1.1.226 in the summer and subsequently by lineage B.1.258 in the fall of the same year. In the winter of 2020 and 2021, lineage B.1.1.7 started to dominate.

In March 2021, the study was announced, and 61 Czech hospitals were contacted. Six hospitals provided the data for the study: Military University Hospital Prague, University Hospital Královské Vinohrady, and University Hospital Ostrava, which are tertiary level academic institutions; České Budějovice Hospital, a tertiary level community institution; and Regional Hospital Nový Jičín and Regional Hospital Náchod, which are district level community institutions. An overview of patients enrolled by individual hospitals is provided in Appendix 2. The data were defined prospectively and included baseline characteristics (age, weight, sex), clinical data (comorbidities, chronic medication, COVID-19 treatment), and outcome data (in-hospital mortality, hospital length of stay, Adaptive COVID-19 Treatment Trial (ACTT-1) scale, number of presumed CP treatment-associated complications). The data were entered into a protected electronic database between March 2021 and February 2022 and consequently used for statistical analysis.

The study group (convalescent plasma group, CP-group) consisted of COVID-19 patients treated with CP, and the control group (non-convalescent plasma group, nCP-group) of COVID-19 patients who did not receive CP. All patients received supportive care according to the study site's standard of care for COVID-19 patients. The standard COVID-19 therapy evolved over the study period and included remdesivir, corticosteroids, immunomodulatory biologic therapy (baricitinib, tocilizumab, sarilumab), and oxygen therapy. Patients received CP for laboratory-confirmed COVID-19 based on the criteria established by the Food and Drug Administration (FDA) [20], and these criteria have been implemented into a national interdisciplinary position statement on the administration of CP in patients with COVID-19 [21]. The patients received up to two units of ABO-matched CP. Each plasma unit of 200 to 250 mL, with a concentration of specific anti-SARS-CoV-2 antibodies ≥ 1:80, determined by the virus-neutralizing test (VNT), was infused over one to two hours. During the infusion, the patients were closely monitored. Vital signs were obtained after the initiation of CP administration and then hourly for the duration of the procedure, and the patients were then closely monitored for any post-infusion reactions for 24 h.

Convalescent plasma was collected at the blood transfusion centers of the participating hospitals in the Czech Republic, which has a decentralized hospital-based system for transfusion services. Apheresis plasma was collected from healthy donors who met the conditions for blood and plasma donation in accordance with Czech and EU legislation and had a low risk of transfusion-related

acute lung injury (TRALI), testing negative for HBsAg, anti-HCV, anti-HIV 1/2, and antibodies against *Treponema pallidum*. Plasma was tested using VNT to detect and determine the titer of neutralizing antibodies against SARS-CoV-2 by observing the cytopathic effect (CPE) on VERO E6 cells, which were seeded in microtiter plates 6 to 24 h before use. Plasma samples were heated to 56 °C for 30 min to inactivate complement and then diluted to final titers of 40, 80, 160, 320, 640, and 1280. SARS-CoV-2 was cultured on VERO E6 cells, with viral replication checked by RT-qPCR. The cultured virus was diluted and transferred to VERO E6 cells in tetraplicates at various dilutions. A suspension of SARS-CoV-2 at 200x TCID50 was added to the plasma, preincubated for 60 min at 37 °C in a CO2 incubator, and then transferred to VERO E6 cells in tetraplicates. Controls included virus-free cell control, virus control on cells, and positive plasma control with a neutralizing antibody titer > 1280. After four days of incubation at 37 °C in a CO_2 incubator, the CPE was evaluated microscopically. The presence of CPE indicated an active virus (absence of neutralizing antibodies), while the absence of CPE indicated the presence of neutralizing antibodies, which protected the cells from viral damage.

Our primary objective was to investigate the effectiveness of CP administration in hospitalized patients aged 18 or older meeting specific criteria such as severity of illness that was classified between three and six points according to the ACTT-1 scale [22] and a Clinical Frailty Scale geriatric frailty score of ≤6 [23]. To address potential confounding variables, we employed propensity score matching based on patient characteristics, including the time interval between symptom onset and CP administration, the patient's condition according to the ACTT-1 scale at hospital admission, the birth year (categorized based on decade: starting from the 1920s up to 1990s), smoking status, and the presence of comorbidities such as cardiovascular disease and ischemic disorders. Propensity score matching, conducted with replacement and three neighbors selected for each matched case, aimed to enhance the comparability of the patients in the intervention group and the patients in the control group. Our investigation focused on the primary outcome of "in-hospital mortality" to evaluate the impact of CP administration in the specified patient population.

The preliminary analysis showed that the effect of administering CP was affected by the timing of CP administration, which was defined as the time between the onset of symptoms and CP administration [24]. The CP-group was further divided into a subgroup of patients in whom CP was used early (early CP-group), defined as patients who were given CP within the first three days since symptom onset, and a subgroup with late CP administration (late CP-group), defined as patients who received CP more than three days after symptom onset. Thus, the key secondary outcome was the influence of the timing of CP administration. The following secondary outcome was the safety of CP treatment, defined as the number of presumed CP-transfusion-associated adverse effects.

A proficient statistician utilized R software (version 4.0.4) for the statistical analyses in this study. Propensity score matching with replacement was employed, wherein three members were iteratively matched to ensure comparability between the CP intervention group and the control group. The groups formed through propensity score matching were then analyzed using logistic regression to determine mortality rates, obtain Kaplan–Meier curves for survival trends, and assess the statistical significance of the difference between the mortality curves using a Cox proportional hazards model. This comprehensive analysis provided insights into the impact of using CP on the survival outcomes in this study population.

Results

A total of 1,498 patients from six centers in the Czech Republic were included in the study, 27.1% ($n=406$) of whom were in the CP-group and 72.9% ($n=1092$) in the nCP-group. The propensity score matching method was used to form the control group, which consisted of 1,218 subjects. Comparisons of the baseline and clinical characteristics, including the clinical status assessment according to the ACTT-1 trial at admission and comorbidities of the CP-group and propensity score-matched group, are detailed in Table 1.

Significant differences between the groups were found for several of the age groups and sex. With regard to comorbidities, only the frequency of diabetes mellitus differed between the groups. For propensity score matching, we included a total of 1,624 patients. The CP-group consisted of 406 patients, of whom 79% ($n=320$) survived. In the nCP-group ($n=1,218$), 62% ($n=751$) of patients survived. This difference was significant regardless of the timing of CP administration ($p<0.001$), according to the logistic regression model Patients who received CP had a median 2.314 times greater chance of survival (odds ratio, OR) (95% confidence interval is 1.78–3.03) than patients who did not receive CP. The relative frequencies and estimates of odds ratios are shown in Table 2. The survival benefit after CP administration is also documented in Fig. 1

For the additional analyses, the CP-group was subdivided into two categories: the early CP-group ($n=100$), comprised of patients who received CP within three days of the onset of disease symptoms, and the late CP-group ($n=306$), consisting of patients who received CP at a later stage of the disease. The comparisons among the groups

Table 1 Baseline and clinical characteristics of the CP-group and propensity-matched nCP-group

		CP-group (*n* = 406)		nCP-group (*n* = 1218)		*p*-value
Baseline (*n*, %)						
age group	60+	287	70,7	884	72,6	0,035
	50–59	58	14,3	142	11,7	0,013
	40–49	39	9,6	133	10,9	0,075
	30–39	17	4,2	17	1,4	< 0.001
	0–30	5	1,2	42	3,4	N/A
sex	males	233	57.4	853	70.0	N/A
	females	173	42.6	365	30.0	< 0.001
Comorbidities (*n*, %)						
body mass index ≥ 30		168	41.0	484	39.7	0.559
cardiovascular diseases		277	68.2	827	67.9	0.902
cardiomyopathy		4	1.0	6	0.5	0.272
heart failure		34	8.4	152	12.5	0.025
hypertension		265	65.3	820	67.3	0.447
coronary artery disease		51	12.6	161	13.2	0.734
diabetes mellitus		127	31.3	487	40.0	0.010
smoking		146	36.0	449	36.9	0.914
COVID-19 severity (*n*, %)						
ACTT-1 on admission	3	45	11.1	142	11.7	N/A
	4	129	31.8	400	32.8	0.931
	5	194	47.8	580	47.6	0.776
	6	34	8.4	96	7.9	0.672
	7	4	1.0	0	0.0	< 0.001
ACTT-1, when considered administration	1	0	0	3	0.2	N/A
	2	0	0	2	0.2	1.000
	3	35	8.6	109	8.9	0.336
	4	104	25.6	333	27.3	0.343
	5	153	37.7	474	38.9	0.330
	6	75	18.5	217	17.8	0.307
	7	37	9.1	79	6.5	0.208
	8	2	0.5	1	0.1	0.060
Day from symptoms at considered administration ≤ 3		100	24,6	329	27.0	0.346
Day from symptoms at considered administration > 3		306	75.4	889	73.0	N/A
Outcome						
in-hospital survival (n, %)		320	78.8	751	61.7	< 0.001
length of hospital stay (days)		15.45	N/A	15.25	N/A	N/A

CP-group, cohort receiving convalescent plasma; nCP-group, control group without administration of convalescent plasma; CP, convalescent plasma; ACTT, Adaptive Covid-19 Treatment Trial; N/A, not applicable

Table 2 Propensity matching, logistic regression, and odds ratio estimate

	total (*n*)	survived (*n*/%)	*p*-value	odds	CI (2.5%)	CI (97.5%)
CP-group	406	320/79	< 0.001	2.314	1.783	3.029
nCP-group	1218	751/62	N/A	N/A	N/A	N/A
early CP-group (up to three days)	100	87/87	0.023	2.097	1.139	4.132
late CP-group (more than four days)	306	233/76	< 0.001	N/A	N/A	N/A
nCP-group	1218	751/62	N/A	0.504	0.376	0.668

CP-group, cohort receiving convalescent plasma; nCP, control group without administration of convalescent plasma; N/A, not applicable

are described in Appendix 1. In the early CP-group, 87% (n=87) of patients survived. In contrast, in the late CP-group, 76% (n=233) of patients survived. The logistic regression model revealed a 2.097-fold greater chance of survival in the early CP-group (95% CI; 1.14–4.13) than in the late CP-group.. Moreover, the survival of both the early CP- and the late CP-groups was significantly better as compared to the nCP-group (p=0.023 for the early CP-group and p<0.001 for the late CP-group). Next, the logistic regression model revealed a highly significant

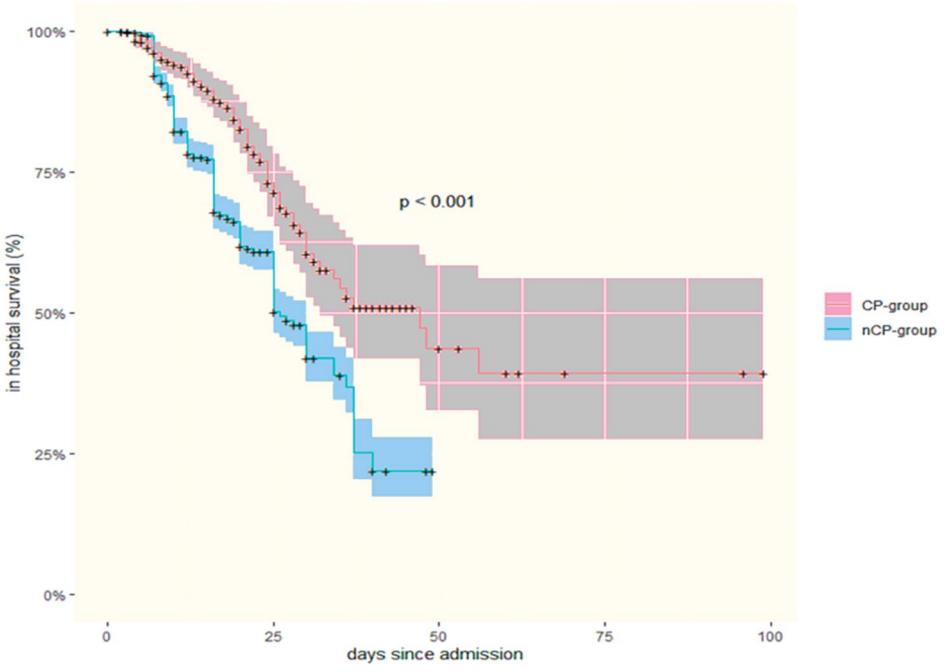

Fig. 1 Kaplan–Meier curves of survival for patients in the CP- and nCP-groups

p value ($p<0.001$) for the coefficient of the late CP-group, emphasizing the statistical importance of the timing of CP administration in predicting patient outcomes. The positive effect of CP administration on survival was also demonstrated by using a competitive logistic regression model along with other predictors. Even in this model, the positive effect of CP was more evident in both the early ($p=0.007$) and late ($p=0.003$) CP-groups than in the nCP-group Regarding the factors obtained for the estimated chance for survival in each group, the chance of survival for the early CP-group was 3.097 (95% CI; 1.38–7.30) times higher compared to that of the nCP-group, and the nCP-group had a survival factor of 0.545 (95% CI; 0.39–0.82) as compared to that in the late CP-group. The survival benefit of the early and the late CP administration is also documented in Fig. 2.

We observed adverse reactions in 9 (2.2%) of the CP-group, and all were of clinically minor severity (Table 3).

Discussion

In this retrospective propensity score-matched analysis, we found that the early administration of CP to COVID-19 patients was associated with significantly improved survival and more rapid recovery than with standard COVID-19 therapy.

The observed mortality benefit of CP in our study aligns with previous prospective trials of CP in COVID-19 patients. In one of the first reports from China, a significant benefit of CP was noted, as 91.3% (21 of 23 patients) of those with severe COVID-19 treated with CP showed clinical improvement compared to 68.2% (15 of 22 patients) who did not receive CP [25]. Similarly, an early case series of 40 COVID-19 patients from five hospitals showed significantly better 14-day survival in severely and critically ill patients when CP was administered early in the disease course [26]. A similar approach was successfully tested in a randomized, double-blind, placebo-controlled trial conducted in Argentina between June and October 2020, when CP was administered within 72 h of the onset of SARS-CoV-2 infection. The results of the modified intention-to-treat analysis in that study showed a significant reduction in the development of severe COVID-19 from 31% (25 of 80 patients) in the placebo arm to 16% (13 of 80 patients) in the CP group [14]. This finding is supported by a systematic meta-analysis of three randomized clinical trials and five matched cohort studies, suggesting that CP therapy in immunocompromised COVID-19 patients is associated with significantly improved survival [27]. However, it is important to note that another study conducted on patients with mild COVID-19 did not show significant differences in survival between 105 patients who received standard therapy and 228 patients who received CP. In that study, the median interval between disease onset and CP administration was eight days, which might represent a significant delay, as passive immunization is recommended early after exposure to infection or early in the course of the infectious disease [16]. Despite the positive results of the abovementioned studies with CP, the routine use of CP in COVID-19 immunocompetent patients

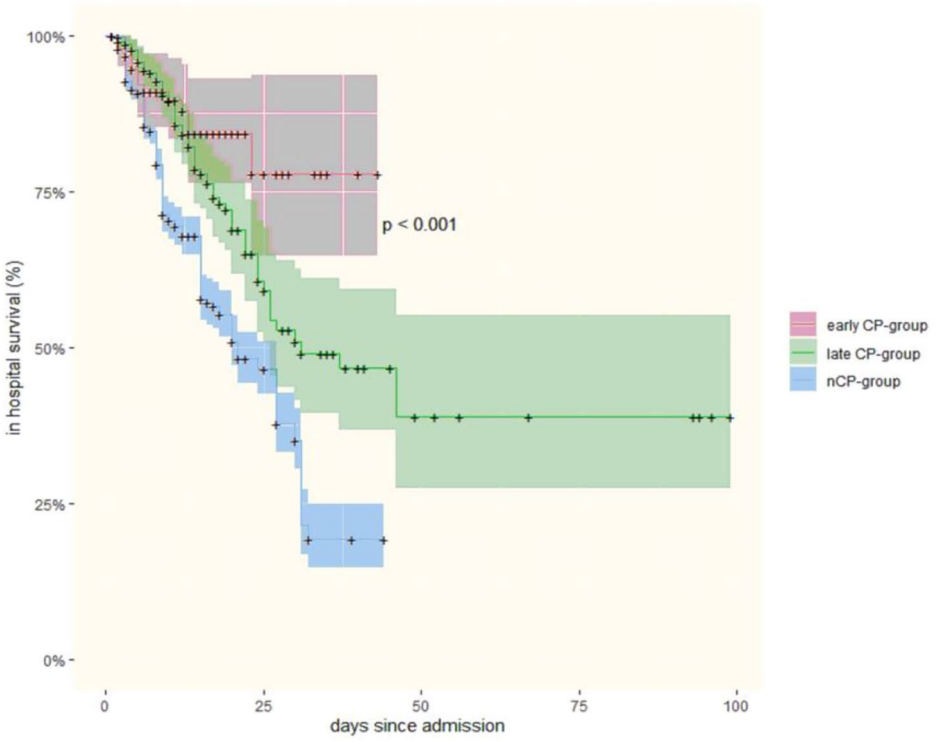

Fig. 2 Kaplan–Meier curves of survival for patients in the early CP-and late CP-groups as compared to that in the nCP-group

Table 3 Adverse reactions after convalescent plasma administration

number of patients enrolled (CP-group) ($n=406$)			
adverse reactions (n, %)	overall	9	2.2
	circulatory overload	4	1.0
	allergic reaction	2	0.5
	febrile reaction	3	0.7

CP, convalescent plasma

is not currently recommended, and CP should only be used as an ambulatory therapy for immunocompromised COVID-19 patients who do not qualify for other prophylactic treatments [28]. This recommendation reflects the decreased virulence of SARS-CoV-2, the strong herd immunity achieved either by natural infection or vaccination, and the availability of efficient antivirals (i.e., remdesivir, molnupiravir, and nirmatrelvir/ritonavir). However, in this context, it should be emphasized that the FDA has stated that monoclonal antibodies (mAb), such as tixagevimab and cilgavimab, are not expected to provide patients with protection against infections from developing SARS-CoV-2 variants. Thus, the use of monoclonal antibodies is limited when the combined national frequency of susceptible SARS-CoV-2 variants is less than or equal to 90% [29]. Therefore, in these situations, CP with high concentrations of anti-SARS-CoV-2 antibodies is still a viable therapeutic approach [28].

This study has certain limitations. First, the retrospective nature of the study does not allow us to definitively conclude that the administration of CP has a positive effect on the survival of COVID-19 patients. However, incorporating a wide range of predictors in propensity score matching enhances the precision of the matching process, resulting in more balanced comparison groups and leading to more robust causal inferences [30]. This approach strongly supports the clinical significance of our results, demonstrating the positive effect of CP on patient survival. Second, the levels of SARS-CoV-2-specific antibodies in the CP used in this study were tested with a non-standardized VNT, which does not allow us to confirm that there is a correlation between the outcomes of COVID-19 patients and the concentration of SARS-CoV-2 neutralizing antibodies in CP. As the final limitation, we would like to mention the potential impact of the different distributions of various oncological diseases in both cohorts (data not shown). Although the percentage representation of oncological diseases differed only minimally (11.8% in the nCP group compared to 13.5% in the CP group), it is a very heterogeneous set for which important data are missing in the database for closer analysis, such as the stage of the disease, type of treatment, its current status, and whether the patient is in remission and if so, for how long. On the other hand, patients with hematological diseases, who can be

expected to have a more severe course of COVID-19 with high probability, accounted for only 2.1% of all included individuals (data not shown), which could have affected our results only negligibly.

In conclusion, our data support CP as an emergency therapy for COVID-19. Our retrospective analysis indicated that CP therapy was associated with improved survival of COVID-19 patients, especially when administered early and to those with a moderate course of the disease. Altogether, CP represents an attractive therapeutic option in certain situations due to its availability, safety, and low cost.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12985-024-02475-y.

Supplementary Material 1

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Author contributions
Conception: MB, MH, JK, JM and PV. Study design: MB, JM, MH. Acquisition of data: PV, JK. Statistical analysis: JK. Data collection: AB, ACH, DK, DŘ, IR, JS, KV, KV, PŠ, RM, RK, SB, VF. Interpretation of the data: MB, MH, JM, JK. Drafted the article: MB, JM, MH. Review of the article and critical revision for important intellectual content: all the authors. Final approval of the submitted version: all the authors.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of the Military University Hospital Prague (registration number: 108/15–87/2020) and by the State Institute for Drug Control (registration number: 2012010001), and it was executed in accordance with the Declaration of Helsinki. Because of the retrospective nature of the study and the use of anonymized data, the need for informed consent was waived by the Ethics Committee.

Consent for publication
All authors have read the manuscript, contributed to it, and approved the authorship and submission.

Competing interests
The authors declare no competing interests.

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