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Clinical trial

Intravenous immunoglobulins for the prevention of postpartum relapses in multiple sclerosis

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ABSTRACT

Objectives: To evaluate the effect of intravenous immunoglobulins (IVIG) on prevention of postpartum relapses in women with relapsing-remitting multiple sclerosis (RRMS).
Methods: This was a retrospective study performed in Ljubljana, Slovenia where the practice for all pregnant women with RRMS is to receive IVIG after the delivery (10 g monthly, during first 6 months after delivery) and in Zagreb, Croatia where no such practice exists. The following data were collected: date of delivery, maternal age at delivery, year of the RRMS diagnosis, EDSS, disease modifying therapy prior to pregnancy, relapses in the year prior, during and in the period of one year after pregnancy.
Results: Data on 132 pregnancies from 112 women (mean age at delivery 31.70 ± 4.10, average disease duration 6.34 ± 4.33) were analyzed. There was no association between the IVIG treatment and annualized relapse rate one year after the delivery (0.27 vs 0.38, rate ratio 1.409, 95% CI 0.764–2.598, $p = 0.272$). No risk factors for the postpartum relapse were identified (age at delivery, duration of RRMS, EDSS prior pregnancy, disease modifying therapy prior pregnancy, relapses in the year prior pregnancy, IVIG).
Conclusion: This study provides no evidence of benefit for postpartum administration of IVIG in women with RRMS.

1. Introduction

Multiple sclerosis (MS) is a disease primarily affecting young women of childbearing potential, making pregnancy related issues an important aspect of patient management. It is well known that pregnancy is a protective factor regarding relapses. However, relapse rates increase in the postpartum period, making it a window of opportunity for therapeutic interventions (Confavreux et al., 1998; Hughes et al., 2014; Paavilainen et al., 2007). These therapeutic interventions have been and still are limited due to breastfeeding and adverse effects of disease modifying therapies (DMTs).

Human immunoglobulins (IVIGs) have been used to reduce postpartum relapse rates in women with relapsing remitting MS (RRMS). The rationale for such practice evolved from the studies showing possible benefits of IVIGs for reducing relapse rates in RRMS (Fazekas et al., 1997; Sorensen et al., 1998; Achiron et al., 1998). There is, however no high quality data available about the efficacy of IVIGs in postpartum women. Only 7 studies reporting original data specifically on the use of IVIGs in postpartum women with RRMS have been published to date (Achiron et al., 1996; Achiron et al., 2004; Haas and Hommes, 2007; Fragoso et al., 2015; Brandt-Wouters et al., 2016; Winkelmann et al., 2018; Hellwig et al., 2009). The treatment regimens differ among these studies, six of them were not blinded and four where retrospective. There was only one double-blinded prospective multicenter clinical trial published, however its primary endpoint was not evaluation of IVIGs efficacy regarding relapse rates in postpartum women with RRMS, but a comparison of two different regimens of IVIG treatment (Haas and Hommes, 2007). Additionally, three of the studies compared their data to a previous study reporting a natural course of the disease in the postpartum period (Haas and Hommes, 2007; Brandt-Wouters et al., 2016; Winkelmann et al., 2018). Out of the seven studies, one did not have the reduction of relapse rate as a primary

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outcome, five showed a positive and one showed a negative effect of IVIG on postpartum relapse rate (Fragoso et al., 2015). Recently published meta-analysis did not support the use of IVIG in postpartum women (Rosa et al., 2018). Furthermore, things might have changed with the advent of DMTs, since it has been shown that the use of DMTs 2 years before pregnancy reduces the risk for postpartum relapses (Hughes et al., 2014).

On the other hand, recently reported data on the impact of pregnancy on relapse rates in women with RRMS did not detect an increased risk for postpartum relapses, an observation possibly attributable to breastfeeding and patients with milder forms of MS being included in the study compared to previously published studies (Langer-Gould et al., 2019).

This leaves us with a limited amount and quality of the available data on the topic, with a consequence of different management strategies of postpartum period in women with RRMS in different MS centers. One example of this is different management in two neighboring MS centers, one in Ljubljana, Slovenia where all women with RRMS receive IVIG after delivery, while in Zagreb, Croatia wait and observe approach is practiced.

We have used this difference to design a retrospective study in order to evaluate the efficacy of IVIGs on postpartum disease course.

2. Methods

This was a retrospective study performed in the University Hospital C1enter Ljubljana, Slovenia and University Hospital C1enter Zagreb, Croatia.

All data were extracted from the hospital electronic charts. If there were missing data, patients were contacted by telephone and additional data were acquired.

Slovenian Medical Ethics Committee and Ethical committee of the University Hospital Center Zagreb approved the study.

2.1. Data extraction

The time frame of 6 years (2013–2018) was included in the analysis. All women with the diagnosis of RRMS and with regular follow-up in the outpatient clinics of both hospitals were eligible for the inclusion in the study. After examination of all women with RRMS, only patients who gave birth were included in the further analysis. Patients with the diagnosis of secondary and primary progressive MS were excluded.

The following data were extracted from the hospital electronic charts from September 2018 till March 2019: age of the patient, year of the RRMS diagnosis, date of delivery, age at delivery, EDSS prior, during and after pregnancy, DMTs prior to pregnancy, relapses in the year prior to pregnancy, relapses during pregnancy, and relapses in the period of one year after pregnancy. Furthermore, MRI data were collected if MRI was available in the period of 12 months after pregnancy. MRI activity was defined if the follow-up MRI showed new or enlarging T2 lesion or T1 lesion with postcontrast enhancement.

2.2. Outcomes

The primary outcome was to investigate whether there is a difference in the annualized relapse rate (ARR) in the first 12 months after the delivery between women with RRMS who received and those who did not receive IVIG postpartally.

Secondary outcomes were:

1 To investigate whether there is a difference in the postpartum MRI activity between women with RRMS who received and those who did not receive IVIG postpartally.
2 To investigate which baseline values may serve as predictors of postpartum relapses.
3 To confirm whether a decreased risk of relapse during pregnancy but significant rebound disease activity in the early postpartum period is present in the studied cohort of women with RRMS.

2.3. Statistical analysis

The Kolmogorov–Smirnov test was applied to test normal distribution. Differences in the distribution of qualitative variables were determined with the Chi-square test (association between the IVIG treatment and number of patients with relapse) and McNemar test (comparison of the number of relapse before, during and after the pregnancy), while the differences in quantitative variables were determined with the use of a parametric *t*-test (age and duration of RRMS) or a non-parametric Mann-Whitney test (EDSS) and Wilcoxon signed ranks test (comparison of ARR in one year prior to pregnancy with ARR during and post-pregnancy). Differences in the number of relapses between the two groups were estimated with the use of Poisson regression model. Univariable Poisson regression analysis was performed to see which variable (age at delivery, duration of RRMS, EDSS prior pregnancy, DMTs therapy prior pregnancy, relapses in the year prior pregnancy and IVIG) has association with the number of relapses one year after the delivery and only variables with $p < 0.2$ were included in multivariable Poisson regression model (relapses in the year prior pregnancy and IVIG). Survival analysis was performed in the form of Kaplan-Meier curves in order to estimate the cumulative risk of patients developing postpartum relapse. Binary logistic regression model was used to determine which variables (age at delivery, duration of RRMS, EDSS prior pregnancy, DMTs therapy prior pregnancy, relapses in the year prior pregnancy and IVIG) are statistically significant predictors for postpartum relapse. Statistical analysis was performed in using the IBM SPSS software, version 25. P values < 0.05 were considered as statistically significant.

3. Results

Data on 132 pregnancies from 112 women with RRMS (mean age at delivery 31.70 ± 4.10, average disease duration 6.34 ± 4.33) were analyzed. Sixty-four of them (48.5%) received IVIG post-delivery (IVIG group) and 68 (51.5%) did not receive IVIG (no-IVIG group). IVIG group had longer disease duration but there was no difference in other baseline characteristics between these two groups ($p > 0.05$). Thirty-nine women (57.4%) received DMT prior to pregnancy in the non-IVIG group (interferon beta (22, 56.4%), glatiramer acetate (8, 20.5%), dimethyl fumarate (2, 5.1%), natalizumab (1, 2.6%), fingolimod (1, 2.6%) and alemtuzumab (5, 12.8%)) and 42 (65.6%) in the IVIG group (interferon beta (21, 50.0%), glatiramer acetate (16, 38.1%), natalizumab (3, 7.1%), fingolimod (1, 2.4%) and rituximab (1, 2.4%)). Reasons why not all women received DMT were reimbursement restrictions and personal choices of the patients. All women stopped taking DMTs prior pregnancy or immediately after confirmation of pregnancy. The baseline characteristics of IVIG and no-IVIG groups are presented in table 1.

3.1. Primary outcomes

There was no statistically significant association between the postpartum relapse and IVIG treatment, where both groups had similar number of patients with postpartum relapses (17 patients had relapses in the non-IVIG group and 19 had relapses in the IVIG group, $p = 0.564$). Univariable Poisson regression analysis was performed to see which variable (age at delivery, duration of RRMS, EDSS prior pregnancy, DMTs therapy prior pregnancy, relapses in the year prior pregnancy and IVIG) has association with the number of relapses one year after the delivery (Supplementary Table 1). Variables with the $p < 0.2$ and IVIG variable were included in the multivariable Poisson regression model (Supplementary Table 2). Based on the multivariable Poisson regression model adjusted to the presence of the relapse in the

Table 1
Baseline characteristics of the no-IVIG and IVIG groups.

	no-IVIG	IVIG	p-value
Age at delivery[#]	31.19 ± 4.31	32.25 ± 3.84	0.139
Duration of RRMS at delivery[#]	5.19 ± 3.23	7.58 ± 5.00	0.002*
EDSS prior pregnancy [±]	1 (0.0–4.0)	1 (0.0–6.5)	0.854
EDSS during pregnancy [±]	1 (0.0–8.0)	1 (0.0–6.5)	0.805
Patients with relapses in the year prior to pregnancy[%]	10 (14.7%)	16 (25%)	0.189
Patients with relapses during pregnancy	7 (10.3%)	6 (9.4%)	1.000
	Rate ratio (95% CI), p -value**		
ARR in the year prior to pregnancy[#]	0.15 ± 0.36	0.31 ± 0.59	2.125 (0.995–4.540), $p = 0.052$
RR during pregnancy[#]	0.13 ± 0.42	0.11 ± 0.36	0.826 (0.308–2.219), $p = 0.705$

* statistically significant at $p < 0.05$.
[#] average ± st.deviation;.
[±] median (min-max);.
[%] number of patients (percentage) ARR annualized relapse rate, RR relapse rate.
** Poisson regression model.

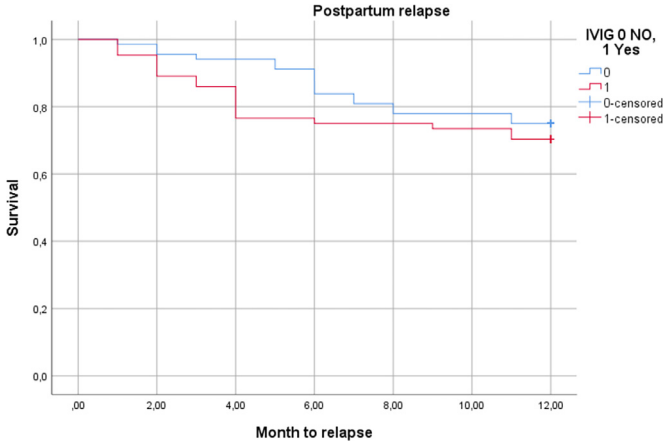

Fig. 1. Kaplan–Mayer curve presenting relapse free survival in months after the delivery.

one year prior to the pregnancy, there was no association between the IVIG treatment and ARR one year after the delivery, showing that both groups had similar ARR (0.27 vs 0.38, rate ratio 1.409, 95% CI 0.764–2.598, $p = 0.272$). A Kaplan-Mayer curve relapse free survival in the months after the delivery for two groups is presented in Fig. 1.

3.2. Secondary outcomes

Other postpartum characteristics of both groups are presented in Table 2.

In the no-IVIG group 42 women (61.8%) and in the IVIG group 52 women (81.3%) performed at least one MRI in the period of 12 months after pregnancy. There was a statistically significant association between the postpartum MRI activity and IVIG treatment, where IVIG group had lower number of patients with active MRI in period of 12 months after the delivery. There was no statistically significant difference in the time to the active MRI between two groups.

Logistic regression analysis showed that age at delivery, duration of RRMS, EDSS prior pregnancy, DMTs therapy prior pregnancy, relapses in the year prior pregnancy and IVIG were not statistically significant risk factors for the occurrence of postpartum relapse (Fig. 2).

Finally, we wanted to confirm whether a decreased risk of relapse during pregnancy and significant rebound disease activity in the early postpartum period are present in the studied cohort of women with RRMS (Fig. 3). There was a statistically significant difference in the proportion of patients with a relapse before and during the pregnancy, where significant number of patients, who had a relapse before the pregnancy, were relapse-free during the pregnancy (19.7% had relapse

Table 2
Postpartum characteristics of the no-IVIG and IVIG groups.

		no-IVIG	IVIG	p-value
Patients with relapses in the first year after the delivery[%]		17 (25%)	19 (29.7%)	0.564
ARR in the first year after the delivery[#]		0.26 ± 0.48	0.39 ± 0.68	0.208**
Month of the first relapse after the delivery [±]		6 (1–11)	4 (1–11)	0.038*
Number of relapses in the first year after the delivery[%]	1	16 (23.5%)	14 (21.9%)	0.386
	2	1 (1.5%)	4 (6.3%)	
	3	0	1 (1.5%)	
Time of the MR [±]		6 (1–12)	9 (1–11)	0.476
Patients with active MRI in the first year after the delivery[%]		20 (47.6%)	11 (21.2%)	0.008*

* statistically significant at $p < 0.05$.
[±] median (min-max);.
[%] number of patients (percentage) (In the no-IVIG group, 42 women (61.8%) and in the IVIG group 52 women (81.3%) performed at least one MRI in the period of 12 months after pregnancy) ARR annualized relapse rate.
** Poisson regression model.

before the pregnancy, 9.8% during the pregnancy, and 15.2% had relapse only before the pregnancy, but not during). There was no statistically significant difference in the proportion of patients with relapse before and after the pregnancy, but there was a statistically significant difference in proportion of patients with relapse during and after the pregnancy, where a significant proportion of patients who were relapse-free during the pregnancy, had relapses after the pregnancy (15.2% had relapse during the pregnancy, 27.3% had relapse after the pregnancy, and 25% had relapse after the pregnancy, but not during) (Table 3).

There was a statistically significant difference between the ARR in the year prior to pregnancy and the ARR during the 2ndtrimester of pregnancy, but there was no statistically significant difference between the ARR prior the pregnancy and the ARR during other trimesters related to pregnancy (Fig. 3).

4. Discussion

Results of the present study showed no effect of postpartum IVIGs on relapse rates in the first year after the delivery. Although most of the so far published studies reported positive results of IVIG on the occurrence of postpartum relapses, there are several differences compared to our study that may explain contradictory results. The most obvious one is a difference in the studied patients regarding the ARR. In all studies showing positive results of IVIG (Achiron et al., 1996; Achiron et al., 2004; Brandt-Wouters et al., 2016; Winkelmann et al., 2018; Hellwig et al., 2009), the ARR in the year prior to pregnancy was much higher compared to our cohort. Pre-pregnancy relapse rates in our

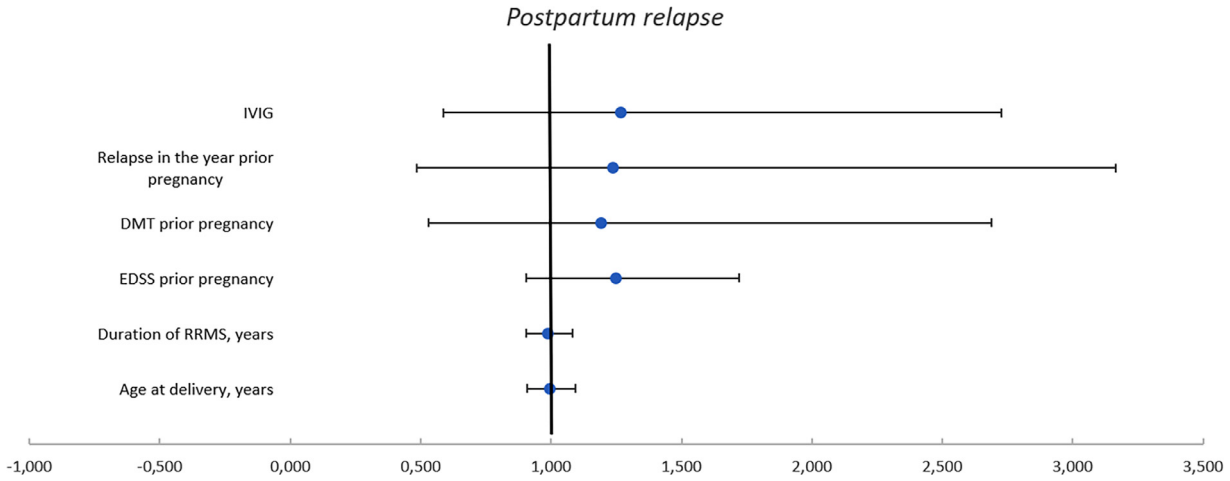

Fig. 2. Result of the logistic regression for predictors of postpartum relapse.

cohort were lower compared to the report from pre-treatment era (Confavreux et al., 1998) and slightly higher compared to recent reports where women on DMTs were included (Hughes et al., 2014). This might be because of earlier diagnosis of possibly milder forms of MS at present due to evolution of MS diagnostic criteria (Rosenkranz et al., 2017). Additionally, only women with milder forms of MS might have decided to give birth. Another important difference is that there were significant differences in previous use of disease modifying therapy between studies, with relatively high proportion of women on higher efficacy disease modifying therapy in our study (12 women (14.8%) in our study were on high efficacy DMT prior pregnancy). Additionally, although pre-pregnancy ARR, DMTs use and EDSS > 2 have been found to represent significantly higher risk for postpartum relapses (Hughes et al., 2014), we were not able to replicate these findings in our cohort.

On the other hand, results of the MRI activity differ from the relapse rate results. Higher percentage of women in the no-IVIG group

Table 3
Comparison of proportions of patients with a relapse before, during and after the pregnancy.

		During pregnancy		P value
		No	Yes	
Before pregnancy	No	99 (75.0%)	7 (5.3%)	0.021*
	Yes	20 (15.2%)	6 (4.5%)	
		After pregnancy		
		No	Yes	
Before pregnancy	No	78 (59.1%)	28 (21.2%)	0.185
	Yes	18 (13.6%)	8 (6.1%)	
		After pregnancy		
		No	Yes	
During pregnancy	No	86 (65.1%)	33 (25.0%)	0.001*
	Yes	10 (7.6%)	3 (2.3%)	

* statistically significant at $p < 0.05$.

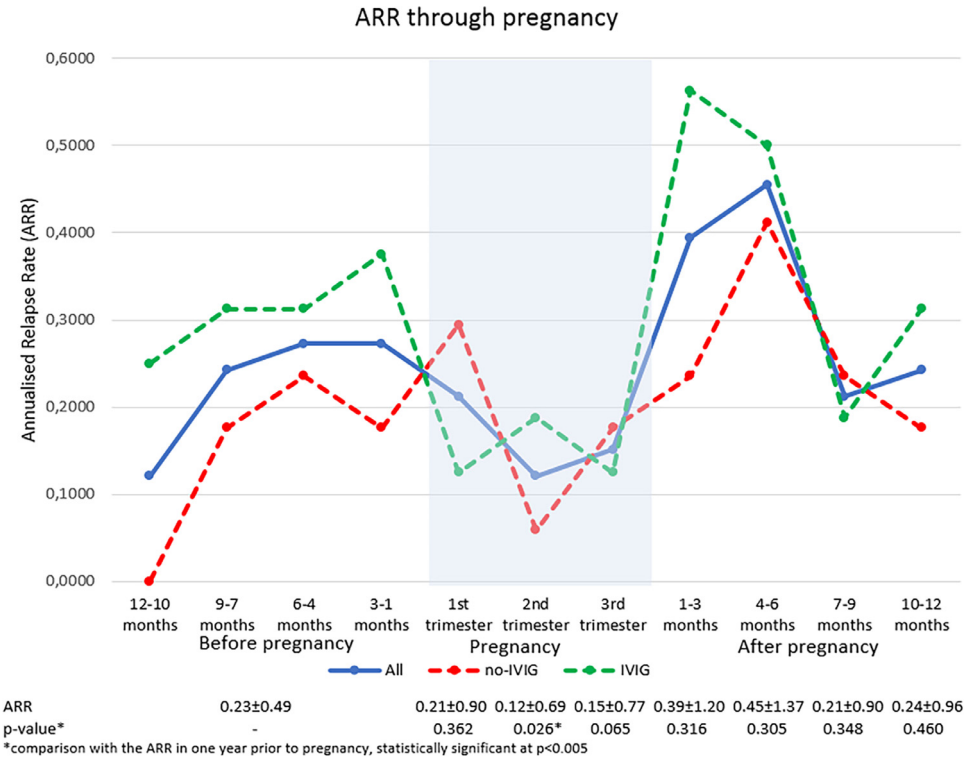

Fig. 3. Annualized relapse rates (ARR) before, during and after pregnancy.

compared to the IVIG group had active MRI in the first year after delivery. Several reasons could contribute to such observation. The most obvious conclusion is that IVIGs are effective in prevention of subclinical inflammatory activity postpartally. This is supported by the studies showing IVIGs reduce MRI activity in non-pregnant women with relapsing multiple sclerosis (Fazekas et al., 1997; Sorensen et al., 1998; Achiron et al., 1998). However, there are cofounding factors possibly contributing to such observations, one being the lack of standardized protocol for MRI follow up in terms of timing for the obvious reason of a retrospective design of the study. This might result in higher number of active MRIs in IVIG group where higher proportion of patients performed MRI in the postpartum period. Additionally, methods for MRI assessments were not standardized; the scanners are different in both centers, as are the protocols, and different radiologists were reporting the results. Additionally, lower percentage of women performed MRI within a year after delivery in the no-IVIG group, so we might miss the opportunity to detect subclinical activity in these women (Paavilainen et al., 2007). All this makes it hard for us to draw conclusions regarding the effect of IVIGs on postpartum MRI activity from our data.

A recent report questioned the rebound in the post-partum relapse rates (Langer-Gould et al., 2019). The lack of increased risk for postpartum relapses was suggested to be a consequence of different baseline characteristics of the studied populations (earlier MS in recent reports) as well as higher rates of breastfeeding. In contrast to these reports we observed a rebound in the relapse activity in the first 6 months after delivery with returning to pre-pregnancy relapse rates after 6 months. Similar results have been observed in previous studies (Confavreux et al., 1998; Hughes et al., 2014; Paavilainen et al., 2007; Houtchens et al., 2018), making the recently questioned rebound activity still highly possible.

This study has limitations pertinent to the retrospective design. Furthermore, a significant proportion of patients did not perform the MRI in the period of 12 months after delivery, which may have led to higher proportion of patients with active MRI in the IVIG group. Finally, due to retrospective design of the study we could not obtain data on the breastfeeding, which might influence the results. Nevertheless, this study included a relatively large number of contemporary pregnant women with MS, where the choice of the treatment was not patient-related leading to a highly comparable groups making the results relevant in the real life setting.

To conclude, we find the use of IVIGs to reduce postpartum relapse rates unjustified due to no effect on the ARR. Following the results, the practice has already been abandoned in Slovenia. The postpartum period remains a period of a higher relapse risk and special care is therefore needed. Women are instructed to breastfeed normally and start DMTs as soon as possible once the breastfeeding phase is over. In patients with a highly active disease other possibilities (immune reconstitution therapies) are now available making pregnancy planning crucial for good outcomes of the pregnancy related disease activity control. Real world data and possible studies might also address the question of a possibility to use therapies with short term child exposure but longer term efficacy in the postpartum/breastfeeding period.

CRediT authorship contribution statement

Alenka Horvat Ledinek: Data curation, Investigation, Writing - review & editing. **Gregor Brecl Jakob:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing - original draft, Writing - review & editing. **Jana Jerše:** Data curation, Investigation, Writing - review & editing. **Berislav Ruška:** Data curation, Investigation, Writing - review & editing. **Tin Pavičić:** Data curation, Investigation, Writing - review & editing. **Tereza Gabelić:** Data curation, Investigation, Writing - review & editing. **Barbara Barun:** Data curation, Investigation, Writing - review & editing. **Ivan Adamec:** Data curation, Investigation, Writing - review & editing. **Uroš Rot:** Data curation, Investigation, Writing - review & editing. **Saša Šega Jazbec:** Data curation, Investigation, Writing - review & editing. **Magdalena Krbot Skorić:** Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing - original draft, Writing - review & editing. **Mario Habek:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing - original draft, Writing - review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2019.101519.

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