Образац **4.**

Факултет Фармацеутски

УНИВЕРЗИТЕТ У БЕОГРАДУ

01 број 1528/1-2
(Број захтева)

Већу научних области медицинских наука
(Назив већа научне области коме се захтев упућује)

18.06.2026.
(Датум)

З А Х Т Е В

за давање сагласности на одлук**е** о усвајању извештаја Комисије за оцену докторске дисертације и о именовању комисије за одбрану

Молимо да, сходно члану 47. ст. 5. тач. 4. Статута Универзитета у Београду ("Гласник Универзитет", број 186/15-пречишћени текст и 189/16), дате сагласност на одлуку о усвајању извештаја Комисије за оцену докторске дисертације:

КАНДИДАТ **ИВАНА (ЈОСИП) СТЕВИЋ**
(име, име једног од родитеља и презиме)

студент докторских студија на студијском програму ДОКТОРСКЕ АКАДЕМСКЕ СТУДИЈЕ- ФАРМАЦЕУТСКЕ НАУКЕ-СОЦИЈАЛНА ФАРМАЦИЈА И ИСТРАЖИВАЊЕ ФАРМАЦЕУТСКЕ ПРАКСЕ

пријавио је докторску дисертацију под називом:

„Фармакоепидемиолошки и фармакоекономски аспекти цитопенија узрокованих применом лекова“

из научне области: СОЦИЈАЛНА ФАРАМАЦИЈА И ИСТРАЖИВАЊЕ ФАРМАЦЕУТСКЕ ПРАКСЕ

Универзитет је дана 28.01.2025.године својим актом под бр. 02-01 број 61206-270/2-25 дао сагласност на предлог теме докторске дисертације која је гласила:

„Фармакоепидемиолошки и фармакоекономски аспекти цитопенија узрокованих применом лекова“

Име и презиме ментора :
1.Др сц. Драгана Лакић, редовни професор, Универзитет у Београду – Фармацеутски факултет (Ужа научна област: Социјална фармација и фармацеутска пракса)
2.Др сц. Валентина Маринковић, редовни професор, Универзитет у Београду – Фармацеутски факултет (Ужа научна област: Социјална фармација и фармацеутска пракса)

Комисија за оцену докторске дисертације именована је на седници одржаној 09.04.2026.године одлуком факултета под бр. 01 бр.812/2 **,** у саставу:

Име и презиме члана комисије	звање	научна област	Установа у којој је запослен

1. Др сц. Душанка Крајновић, редовни професор, Универзитет у Београду – Фармацеутски факултет (ужа научна област: Социјална фармација и фармацеутска пракса), председник Комисије
2. Др сц. Слободан Јанковић, редовни професор, Универзитет у Крагујевцу – Факултет медицинских наука (ужа научна област: Фармакологија са токсикологијом; клиничка фармација)
3. Др сц. Марина Одаловић, редовни професор, Универзитет у Београду – Фармацеутски факултет (ужа научна област: Социјална фармација и фармацеутска пракса)

Напомена**:** уколико је члан Комисије у пензији навести датум пензионисања.

Датум стављања извештаја Комисије и докторске дисертације на увид јавности: 14.05.2026.године.

Наставно-научно веће факултета усвојило је извештај Комисије за оцену докторске дисертације наседници одржаној дана 18.06.2026.године.

Комисија за одбрану докторске дисертације именована је на седници одржаној 09.04.2026.године

одлуком факултета под бр. 01 број 812/2, у саставу:

Име и презиме члана комисије	звање	научна област	Установа у којој је запослен

4. Др сц. Душанка Крајновић, редовни професор, Универзитет у Београду – Фармацеутски факултет (ужа научна област: Социјална фармација и фармацеутска пракса), председник Комисије
5. Др сц. Слободан Јанковић, редовни професор, Универзитет у Крагујевцу – Факултет медицинских наука (ужа научна област: Фармакологија са токсикологијом; клиничка фармација)
6. Др сц. Марина Одаловић, редовни професор, Универзитет у Београду – Фармацеутски факултет (ужа научна област: Социјална фармација и фармацеутска пракса)

Напомена: уколико је члан Комисије у пензији навести датум пензионисања.

ДЕКАН ФАКУЛТЕТА

Прилози:
1. Одлука Наставно-научног већа о усвајању извештаја Комисије за оцену докторске дисертације и одлука о именовању Комисије за одбрану докторске дисертације
2. Извештај Комисије о оцени докторске дисертације
3. Примедбе на извештај Комисије о оцени докторске дисертације (уколико их је било) и мишљење Комисије о примедбама

Напомена: Факултет доставља Универзитету захтев са прилозима у електронској форми и у једном писаном примерку за архиву Универзитета

УНИВЕРЗИТЕТ У БЕОГРАДУ
ФАРМАЦЕУТСКИ ФАКУЛТЕТ
11000 - БЕОГРАД
Ул. Војводе Степе 450.
01. број 1528/1
18.06.2026. године

На основу члана 28. Статута и предлога Комисије за последипломске студије – докторске студије, Наставно-научно веће Универзитета у Београду – Фармацеутског факултета на седници одржаној 18.06.2026.године, донело је

О Д Л У К У

ПРИХВАТА СЕ позитиван извештај Комисије за оцену и одбрану завршене докторске дисертације**,** кандидата **маг. фарм. Ивана Стевић** под насловом: **„Фармакоепидемиолошки и фармакоекономски аспекти цитопенија узрокованих применом лекова“** и упућује Већу научних области медицинских наука на усвајање, а по добијеној писаној сагласности одобрава јавна одбрана пред Комисијом у саставу:

Комисија за оцену и одбрану завршене докторске дисертације у саставу:

1. Др сц. Душанка Крајновић, редовни професор, Универзитет у Београду – Фармацеутски факултет (ужа научна област: Социјална фармација и фармацеутска пракса), председник Комисије
2. Др сц. Слободан Јанковић, редовни професор, Универзитет у Крагујевцу – Факултет медицинских наука (ужа научна област: Фармакологија са токсикологијом; клиничка фармација)
3. Др сц. Марина Одаловић, редовни професор, Универзитет у Београду – Фармацеутски факултет (ужа научна област: Социјална фармација и фармацеутска пракса)

Универзитет је дана 28.01.2025.године својим актом бр.: 02-01 бр: 61206-270/2-25 дао сагласност на предлог теме докторске дисертације.

Кандидат маг. фарм. спец. Ивана Стевић, објавила је резултате из ове докторске дисертације у једном раду категорије М21а, једном раду категорије М21 и једном раду категорије М22 у међународним часописима са СЦИ листе:

1. **Stević** I, Janković SM, Mihailović M, Jović I, Odalović M, Marinković V, Lakić D. Cytopenias as Adverse Drug Reactions: A 10-Year Analysis of Reporting Structure, Rate, and Trend. Pharmaceuticals (Basel). 2025 Dec 20;19(1):14. doi: 10.3390/ph19010014.
   Област: Pharmacology & Pharmacy
   Импакт фактор: IF2 (2024) = 4,8 (51/352); IF5 (2024) = 4,9 (58/344) **M21a**
2. **Stević I,** Janković SM, Georgiev AM, Marinković V, Lakić D. Factors associated with hematological adverse reactions of drugs authorized via the centralized procedure. Sci Rep. 2024 Apr 20;14(1):9074. doi: 10.1038/s41598-024-59710-3.
   Област: Multidisciplinary sciences
   Импакт фактор: IF2 (2024) = 3,9 (25/136); IF5 (2024) = 4,3 (25/135) **M21**

3. **Stević I**, Janković SM, Petrović N, Čanak-Baltić N, Marinković V, Lakić D. Nonchemotherapy drug-induced cytopenias: A cost-of-illness study using the microcosting methodology based on real-world data. Br J Clin Pharmacol. 2025 Jun 11. doi: 10.1002/bcp.70122. Epub ahead of print.
   Област: Pharmacology & Pharmacy
   Импакт фактор: IF2 (2024) = 3,0 (138/352); IF5 (2024) = 3,4 (129/344) **M22**

Одлуку доставити: кандидату, Универзитету, члановима комисије, декану, секретару, продекану за последипломске студије, ментору (проф др. Драгана Лакић и проф.др.Валентина Маринковић), Одсеку за наставу и студентска питања, Одсеку за правне и опште послове, пословном секретару, председнику Комисије за последипломске студије – докторске студије (Проф. др Биљана Антонијевић) и архиви.

ПРЕДСЕДНИК
НАСТАВНО-НАУЧНОГ ВЕЋА
ФАРМАЦЕУТСКОГ
ФАКУЛТЕТА

Проф. др Наташа Богавац Станојевић

НАСТАВНО-НАУЧНОМ ВЕЋУ
ФАРМАЦЕУТСКОГ ФАКУЛТЕТА УНИВЕРЗИТЕТА У БЕОГРАДУ

КОМИСИЈИ ЗА ПОСЛЕДИПЛОМСКУ НАСТАВУ – ДОКТОРСКЕ СТУДИЈЕ

На седници Наставно-научног већа Фармацеутског факултета Универзитета у Београду, одржаној 09. априла 2026. године (одлука бр. 812/2), именовани су чланови Комисије за оцену и одбрану завршене докторске дисертације кандидата маг. фарм. спец. Иване Стевић, под насловом: **„Фармакоепидемиолошки и фармакоекономски аспекти цитопенија узрокованих применом лекова”**. Ова докторска теза урађена је под менторством др. сц. Драгане Лакић, редовног професора Универзитета у Београду – Фармацеутски факултет и др. сц. Валентине Маринковић, редовног професора Универзитета у Београду – Фармацеутски факултет.

Чланови комисије за оцену и одбрану докторске дисертације у саставу:

1. **Др сц. Душанка Крајновић**, редовни професор, Универзитет у Београду – Фармацеутски факултет (ужа научна област: Социјална фармација и фармацеутска пракса), председник Комисије

2. **Др сц. Слободан Јанковић**, редовни професор, Универзитет у Крагујевцу – Факултет медицинских наука (ужа научна област: Фармакологија са токсикологијом; клиничка фармација)

3. **Др сц. Марина Одаловић**, редовни професор, Универзитет у Београду – Фармацеутски факултет (ужа научна област: Социјална фармација и фармацеутска пракса)

прегледали су приложену дисертацију и пропратну документацију и подносе Наставно-научном већу Универзитета у Београду – Фармацеутског факултета следећи:

ИЗВЕШТАЈ

Кандидат Ивана Ј. Стевић рођена је 22. априла 1990. године у Горњем Милановцу, где је завршила основну и средњу школу. Интегрисане академске студије завршила је 2016. године на Универзитету у Београду – Фармацеутском факултету, а на истом факултету је завршила и специјалистичке академске студије из области Фармакоекономије и фармацеутске легислативе (2018. године), и из области Фармацеутског менаџмента и маркетинга (2022. године). Кандидат има више од десет година радног искуства на

различитим позицијама у области регулативе, маркетинга и политике цена фармацеутских производа у домаћим и страним компанијама, а од новембра 2020. године запослена је на Фармацеутском факултету (на Катедри за социјалну фармацију и фармацеутско законодавство).

1. ПРИКАЗ САДРЖАЈА ДОКТОРСКЕ ДИСЕРТАЦИЈЕ

Докторска дисертација кандидата Иване Стевић под насловом „Фармакоепидемиолошки и фармакоекономски аспекти цитопенија узрокованих применом лекова“, написана је јасним и прегледним стилом на 139 страна, формата А4, фонтом *Times New Roman,* величине 12 и једноструким проредом. У склопу дисертације приказано је укупно 32 табеле, 30 слика и 262 литературна навода. Дисертација садржи следећа поглавља: Увод, Циљеви, Методологија, Резултати, Дискусија, Закључци и Литература.
На почетку дисертације представљен је Сажетак рада на српском и енглеском језику и садржај, док се на крају налази седам прилога, кратка биографија кандидата и потписане изјаве кандидата о ауторству, истоветности штампане и електронске верзије и коришћењу докторске дисертације.

Увод докторске дисертације садржи свеобухватан преглед релевантних литературних података о нежељеним реакцијама на лекове (НРЛ), са освртом на хематолошке НРЛ, односно на цитопеније (анемија, леукопенија, тромбоцитопенија) које су узроковане применом лекова. У уводу је наведена дефиниција НРЛ која је у складу са литературом, европским регулаторним оквиром и законском регулативом у Србији. Наведена је класификација цитопенија као НРЛ према типу и механизму настанка, уз приказ дефиниција и граничних вредности за сваку врсту цитопеније, и дат је преглед лекова за које је у литератури познато да могу да их изазову.

У уводу је у одељку који се односи на фармакоепидемиолошки аспект, на основу доступних података приказана учесталост појаве НРЛ и цитопенија као посебне врсте, затим образложена је важност постмаркетиншког праћења безбедности лекова и система фармаковигиланце са освртом на изазове препознавања и пријављивања НРЛ, са посебним фокусом на цитопеније као НРЛ. Описана је улога регулаторног тела у националном систему фармаковигиланце и његова повезаност са глобалним системима праћења безбедности лекова (*Upsala Monitoring Center*). Препознато је да је и поред постојећих обавеза пријављивања, степен пријављивања НРЛ – а посебно цитопенија – значајно низак, те да у литератури недостају прецизни подаци о учесталости, структури и трендовима пријављивања ових поремећаја на националном и глобалном нивоу.

У уводу је у одељку који се односи на фармакоекономски аспект, приказан и финансијски (економски) аспект оптерећења здравственог система и друштва које су последице НРЛ уопштено, као и оптерећења које је последица посебне групе НРЛ односно цитопенија, са

освртом на постојеће студије трошкова које су углавном биле фокусиране на антиканцерске лекове или на појединачне лекове у случају лекова који не припадају групи антиканцерских лекова. Указано је на недостатак студија трошкова болести заснованих на микротрошковном приступу за цитопеније узроковане лековима који не припадају групи антиканцерских лекова.

У наставку увода изложени су основни концепти здравствене економије и фармакоекономских анализа, укључујући врсте трошкова, перспективе, врсте фармакоекономских студија, као и основни концепти приказа резултата фармакоекономских евалуација. Описан је здравствени систем и систем здравственог осигурања у Србији, са улогом Републичког фонда за здравствено осигурање (РФЗО).

На крају увода јасно је образложена потреба за истраживањима у области фармакоепидемиологије и фармакоекономије цитопенија узрокованих применом како антиканцерских лекова, тако и лекова који не припадају групи ових лекова, како би се унапредила савремена клиничка пракса, фармаковигиланца ових НРЛ и доношење одлука у процесу лечења пацијената. Циљеви истраживања у оквиру ове докторске дисертације постављени су у односу на налазе у литератури који указују на потребе за додатним истраживањима у области фармакоепидемиологије и фармакоекономије, а на основу јасно препознатог недостатка прецизних података о учесталости, структури и трендовима пријављивања цитопенија на националном и глобалном нивоу, као и недостатка студија трошкова цитопенија узрокованих лековима који не припадају групи антиканцерских лекова и фармакоекономских анализа лечења ових поремећаја (хипотеза истраживања).

Циљеви истраживања су јасно дефинисани и подељени на четири целине:

1. Анализа повезаности регулаторних фактора и учесталости очекиваних цитопенија узрокованих применом лекова (антиканцерских лекова и лекова који не припадају групи антиканцерских лекова);

2. Анализа пријава нежељених реакција на лек типа цитопенија на глобалном нивоу;

3. Анализа трошкова лечења цитопенија узрокованих применом лекова који не припадају групи антиканцерских лекова у Републици Србији;

4. Фармакоекономска евалуација лечења цитопенија (анемије, леукопеније и тромбоцитопеније) које су узроковане применом лекова који не припадају групи антиканцерских лекова.

У поглављу **Методологија,** наведено је да су коришћени разноврсни научни методи: за први и други циљ - секундарна анализа постојећих база података, за трећи циљ: студија трошкова болести по типу студија пресека, за четврти циљ: израда фармакоекономских модела. За спровођење дефинисаних циљева добијена су сва неопходна одобрења етичких комитета односно одбора и сагласност регулаторног тела (Агенције за лекове и

медицинска средства Србије – АЛИМС) за употребу података за израду докторске дисертације.

За први циљ детаљно је описано истраживање секундарног типа које је засновано на јавно доступним информацијама, односно на базама регистрованих лекова и листе есенцијалних лекова Светске Здравствене Организације (СЗО). Детаљно је описан поступак формирања сетова података за анализу (по заштићеном имену, интернационалном незаштићеном имену (ИНН), за биолошке лекове и биосимиларе). Наведене су зависне и независне варијабле студије, као и статистичке методе – дескриптивна статистика, мултиваријантна бинарна логистичка регресиона анализа са методом обрнутог условног уклањања предиктора, и модел дрвета одлучивања за класификацију лекова према ризику од појаве очекиваних хематолошких НРЛ.

За други циљ, описана је методологија секундарне анализе података добијених из глобалне базе спонтаних пријава НРЛ – *VigiBase* – за десетогодишњи период (2014–2023), како на глобалном нивоу тако и за Србију. Детаљно су приказане екстраховане варијабле за структуру пријављених случајева, као и методологија израчунавања годишње стопе пријављивања и анализе тренда применом методе *joinpoint* регресије. Описан је и поступак анализе комплетности информација о потреби за праћењем цитопенија која је наведена у сажецима карактеристика лека (СКЛ) за оне лекове код којих је уочено у резултатима првог циља да се цитопеније јављају са учесталошћу "веома често".

За трећи циљ детаљно је описана студија трошкова болести (енгл. *cost-of-illness, COI*) која је спроведена применом микротрошковне анализе приступом "одоздо ка горе", као златног стандарда за овај тип студије. Подаци су прикупљени ретроспективно из реалног окружења на терцијарном нивоу здравствене заштите (Клинички универзитетски центар Крагујевац), за период 2020–2022. Јасно су дефинисани критеријуми за укључивање и искључивање пацијената, описан је процес узорковања (селекције случајева), а наведен је и коначан број случајева по врсти цитопеније (46 леукопенија, 71 анемија, 80 тромбоцитопенија). Приказане су варијабле од интереса и методологија израчунавања директних и индиректних трошкова, са образложењем перспективе платиоца (РФЗО, пацијент, послодавац), као и начин изражавања трошкова за потребе међународног поређења. Описана је и статистичка анализа, укључујући генерализовани линеарни модел за утврђивање предиктора укупног трошка лечења.

За четврти циљ описане су фармакоекономске анализе односа трошкова и ефеката (енгл. *cost-effectiveness analysis,* CEA) и односа трошкова и користи (енгл. *cost-utility analysis* CUA), које су спроведене за сваку врсту цитопеније посебно (анемију, леукопенију и тромбоцитопенију), применом модела дрва одлуке. Детаљно су образложени избори поредбених стратегија, извори података за трошкове, вероватноће за поједине догађаје, ефективност поредбених стратегија и вредности квалитета живота. Наведено је да су анализе спроведене из перспективе РФЗО-а, уз примену Монте Карло симулације, и спроведену једнострану анализу сензитивности са графичким приказом резултата кроз

Торнадо дијаграм. Резултати су приказани у складу са *CHEERS* водичем за извештавање о економским евалуацијама.

Дискусија је обухватила анализу и разматрање добијених резултата са критичким осртом на резултате сличних истраживања. Наведене су предности и ограничења истраживања у оквиру дисертације, као и смернице за даља истраживања у овој области.

Поглавље **Закључци** садржи сажето приказане најважније закључке проистекле из резултата истраживања, а који су у складу са претходно постављеним циљевима.

У оквиру поглавља **Литература** наведено је 262 референце које су коришћене током израде докторске дисертације.

Прилози садрже наведена додатна и потребна документа, укључујући списак скраћеница, списак табела, као и додатне резултате са 12 табеларних приказа.

Биографија садржи кратку биографију кандидата.

На самом крају докторске дисертације налазе се неопходне изјаве сходно Правилнику о докторским студијама на Универзитету у Београду.

Одлуке Етичке комисије Факултета и остале неопходне етичке одлуке

За спровођење дефинисаних циљева добијена су сва неопходна одобрења етичких комитета односно одбора:

- Етичког комитета Универзитета у Београду – Фармацеутског факултета (2956/2 од 24.12.2024), и
- Етичког одбора Универзитетског клиничког центра Крагујевац (01/22–340 од 10.10.2022)

и сагласност регулаторног тела (Агенције за лекове и медицинска средства Србије – АЛИМС) за употребу података за израду докторске дисертације (март 2026).

2. ОПИС ПОСТИГНУТИХ РЕЗУЛТАТА

У поглављу **Резултати** описани су резултати спрам претходно постављених циљева истраживања.

Први циљ

Анализом 1349 важећих дозвола за лекове одобрених централизованим поступком од стране ЕМА-е (883 јединствених ИНН-ова), утврђено је да је више од половине лекова (54,78%) повезано са очекиваном појавом неке хематолошке НРЛ, а сваки пети лек са њеном веома честом учесталошћу. Анемија, тромбоцитопенија и леукопенија као НРЛ очекиване су код 40,47%, 41,14% и 36,17% лекова, респективно. Лекови из *ATC* групе *L* (антинеопластици и имуномодулатори) су лекови код којих се чешће очекује појава хематолошких НРЛ било које учесталост у односу на друге групе лекова. Мултиваријантном бинарном логистичком регресијом идентификовани су кључни регулаторни фактори повећаног ризика од очекиване појаве хематолошких НРЛ било које учесталости: генерички статус лека (*OR* 1,76–2,37), статус биосимилара (*OR* 3,26–11,25) и присуство на есенцијалној листи лекова СЗО (*OR* 2,08–2,53), док је пут примене лека био једини протективни фактор. За веома честу учесталост хематолошких НРЛ, статус биосимилара, условна дозвола и присуство на есенцијалној листи лекова СЗО показали су се као значајни фактори. На нивоу биосимилара, код лекова истог ИНН-а није утврђена разлика у учесталости појаве хематолошких НРЛ, а разлика у односу на референтне биолошке лекове уочена је само у случају соматропина. Резултати су додатно приказани кроз моделе дрвета одлучивања. У прилогу докторске дисертације су дати додатни резултати из овог дела, укључујући листу лекова на нивоу ИНН-а код којих се јавља специфична цитопенија као нежељена реакција на лек са учесталошћу веома често.

Други циљ

У десетогодишњем периоду (2014–2023) глобално је пријављено укупно 74873 случајева леукопеније, 161631 случај анемије и 141836 случајева тромбоцитопеније као НРЛ, у поређењу са 88, 122 и 126 случајева пријављених у Србији. Утврђене су статистички значајне разлике у структури пријављених случајева између света и Србије за скоро све категорије (старосна група, пол, озбиљност, извештач), при чему је величина ефекта указивала на малу практичну разлику. Цитопеније су најчешће пријављиване код жена, старости 45–64 година, а у Србији је удео пријава од стране лекара значајно виши него у свету (76,34% наспрам 31,72%), уз знатно нижи удео пријава од стране фармацеута. Просечна стопа пријављивања цитопенија у десетогодишњем периоду била је упоредива између света и Србије (4,87 наспрам 4,83 НРЛ/милион/годишње). Анализом тренда утврђен је раст у пријављивању свих типова цитопенија у Србији, уз већу варијабилност у стопама пријављивања у поређењу са светом, што указује на неконзистентност у пракси фармаковигиланце. Анализом комплетности информација у СКЛ-овима лекова утврђено је да је потпуна информација о праћењу цитопенија наведена код мање од две трећине лекова, при чему статистичка анализа није показала значајну повезаност између комплетности информација о праћењу у СКЛ-у и постојања пријаве НРЛ. У прилогу

докторске дисертације је наведен списак лекова (према ИНН-у) за које су најчешће пријављиване цитопеније као НРЛ.

Трећи циљ

У студији су анализирани случајеви цитопенија узрокованих применом лекова који не припадају групи антикацерских лекова (46 леукопенија, 71 анемија, 80 тромбоцитопенија), чиме је испуњен критеријум за минималну величину узорка. Просечна старост пацијената износила је 63,6 ± 16,3 године, већина случајева је забележена код пацијената женског пола, а пацијенти су током хоспитализације лечени у просеку са више од 27 различитих лекова на нивоу ИНН-а, од чега је 15 лекова имало потенцијал да узрокује цитопенију. Просечна дужина хоспитализације била је изнад 25 дана, уз преко 16 прегледа лекара специјалиста. Трансфузија је примењена код више од половине пацијената са анемијом или тромбоцитопенијом, а код тежих облика (степен ≥ 3) код два од три пацијента. Највећи просечни укупни трошкови по случају забележени су за леукопенију (200.928,4 ± 125.838,4 *RSD*), затим за тромбоцитопенију (115.065,2 ± 73.064,2 *RSD*), а најмањи код анемије (109.502,5 ± 68.604,2 *RSD*). Код леукопеније скоро половину укупних трошкова чинили су трошкови лекова (49%), док су код анемије и тромбоцитопеније трошкови хоспитализације највише доприносили укупним трошковима. Мултиваријантна анализа применом генерализованог линеарног модела показала је да је број компјутеризованих томографија једини фактор повезан са укупним трошковима за сва три типа цитопеније, уз додатне специфичне предикторе за сваки тип. Анализа индиректних трошкова указала је на значајну асиметрију у расподели финансијског терета — послодавац сноси 4,3 пута виши дневни индиректни трошак у односу на РФЗО, а пацијент губи просечно 41,2% зараде по епизоди хоспитализације.

Четврти циљ

Фармакоекономске анализе *CEA* и *CUA*, спроведене применом модела дрва одлуке са Монте Карло симулацијом на кохортама од 1000 виртуелних пацијената, показале су да су све три профилактичке стратегије трошковно исплативе (доминантне: нижи трошкови, већа ефективност/корисност) у поређењу са стандардном терапијом. Нето новчани бенефит у случају леукопеније и примене филграстима је био позитиван (нпр. код *CEA* 111.076,17 *RSD*), док је у случају анемије код примене дарбепоетина-алфа био такође позитиван (нпр. код *CUA* 1.763.778,87 *RSD*). Позитиван нето новчани бенефит је добијен и у случају тромбоцитопеније и профилактичке примене фондапаринукса (нпр. код *CEA* 407.224,70 *RSD*). Спроведене анализе сензитивности за сва три типа цитопенија потврдиле су робусност резултата — нето новчани бенефит остао је позитиван и при екстремним варирањима улазних параметара, што је приказано Торнадо дијаграмима.

3. УПОРЕДНА АНАЛИЗА РЕЗУЛТАТА ДИСЕРТАЦИЈЕ СА ПОДАЦИМА ИЗ ЛИТЕРАТУРЕ

У дискусији првог циља је наведено да је по сазнањима аутора ово прва студија која истражује везу између регулаторних фактора и учесталости очекиваних хематолошких и специфичних цитопенија као НРЛ, и прва студија која у потпуности користи јавно доступне податке на нивоу свих лекова одобрених централизованим поступком, без терапијских ограничења или ограничења датума одобрења. Резултати показују да статус биосимилара, генерички статус лека и присуство лека на есенцијалној листи лекова СЗО представљају кључне регулаторне факторе повећаног ризика очекиване појаве хематолошких НРЛ. Утицај пута примене лека као протективног фактора биолошки је образложен избегавањем системске апсорпције и последично занемарљивом изложеношћу коштане сржи, а поткрепљен је налазима *Ingrasciotta* и сарадника у студији о аплазији еритроцита повезаној са применом епоетин-алфа (1). Налаз да је присуство лека на листи есенцијалних лекова СЗО фактор ризика објашњен је захтевима за укључивање на ту листу — лек мора бити у примени дужи низ година, чиме је омогућен добро познат безбедносни профил, а самим тим и виша стопа препознавања и пријављивања НРЛ (2). Статус условне дозволе и додатног праћења лека повезан је са строжим постмаркетиншким обавезама и активнијим надзором (3,4), а налаз да убрзана процена повећава ризик у складу је са другим студијама које показују потенцијалну везу између скраћеног поступка одобравања и безбедносних проблема након стављања лека на тржиште (3). Одсуство протективних регулаторних фактора на нивоу ИНН-а представља важну практичну импликацију — управљање ризиком треба да буде обезбеђено активним клиничким мониторингом комплетне крвне слике, а не ослањањем искључиво на регулаторни статус лека. Поређење са другим студијама које су користиле базу података ЕМА (*Mol* и сар. (3), *Francisca* и сар. (5), *Zeitoun* и сар. (6), *Meregaglia* и сар. (7) указује на снагу ове студије у односу на претходне, будући да оне нису укључивале све лекове, нити су анализирале утицај начина примене и есенцијалне листе лекова СЗО.

Други циљ докторске дисертације био је поређење пријављивања цитопенија у свету и у Србији и показано је да постоје статистички значајне разлике у структури пријава, уз малу практичну величину ефекта. Налаз да је у Србији удео пријава од стране лекара значајно виши него у свету (~76% наспрам ~32%) у складу је са другим публикацијама у којима је пријављивање НРЛ претежно долазило од стране лекара (8-10). Ниска стопа пријављивања цитопенија од стране фармацеута у Србији (1,69%) у поређењу са уделом у глобалном пријављивању (~9%) у складу је са чињеницом да је приступ фармацеута лабораторијским резултатима у Србији ограничен, а студије из Канаде показале су да приступ фармацеута лабораторијским резултатима значајно побољшава квалитет неге и препознавање проблема повезаних са применом лекова (11–14). Већи удео пријављивања у категорији женских пацијената, у радно способном добу (45–64 година) конзистентно је

са другим публикацијама о структури пријављивања НРЛ (10, 15–22), а у складу је и са резултатима *Rademaker*-а да жене имају виши ризик од развоја НРЛ (23). Висок удео озбиљних случајева очекиван је имајући у виду да мање озбиљни поремећаји у броју крвних ћелија често не производе јасну клиничку слику и остају непрепознати (24,25), а у складу је са уделом озбиљних случајева у бази *FAERS* (енгл. *Food and Drug Administration Adverse Event Reporting System*) (26). Тренд раста пријављивања свих типова цитопенија у Србији, уз већу варијабилност у стопама пријављивања него у свету, указује на неконзистентност у пракси фармаковигиланце (24, 27-29), потврђену и резултатима из трећег истраживачког циља ове дисертације – у само једној болници терцијарне здравствене заштите идентификован је 71 случај анемије у трогодишњем периоду, наспрам свега 40 пријава на националном нивоу у десетогодишњем периоду на нивоу целе државе (30). Одсуство статистички значајне повезаности између комплетности информација о праћењу у СКЛ-у и пријављивања НРЛ треба тумачити уз ограничење малог броја пријава по групи, а резултат да 36,6 – 41,4% СКЛ-ова нема потпуну информацију о праћењу крвне слике за лекове код којих је цитопенија наведена као очекивана НРЛ са веома честом учесталошћу, сам по себи је клинички значајан и у складу је са студијом *Ferner* и сарадника (31), која је такође указала на недостатке у информацијама о праћењу хематолошких НРЛ у СКЛ-овима (32–35).

Према резултатима докторске дисертације, *COI* студија је прва која примењује микротрошковну методологију приступом „одоздо ка горе" на цитопеније узроковане применом лекова који не припадају групи антиканцерских лекова, кроз прикупљање података из реалног окружења на нивоу појединачног пацијента. Трошкови по случају цитопеније у Србији (109.502–200.928 *RSD*) кретали су се у опсегу упоредивим са налазима других *COI* студија за специфичне цитопеније (36-38). Дужина хоспитализације идентификована је као главни предиктор укупних трошкова, и то је у складу са налазима других *COI* студија (39-44). Резултат виших индиректних трошкова по послодавцу у односу на РФЗО произлази из законске регулативе у Србији, где послодавац сноси трошак боловања првих 30 дана (45). Методологија ове студије може послужити као основа за будуће мултицентричне студије, будући да тренутно не постоји хармонизована методологија за спровођење микротрошковних студија у овој области (46–49).

Фармакоекономске анализе спроведене у оквиру четвртог циља показале су да су профилактичке стратегије лечења тешких облика свих анализираних цитопенија трошковно исплативе из перспективе РФЗО-а. Доминантност стратегије профилактичке примене филграстима код појаве тешке леукопеније је у складу са литературним налазима о трошковној исплативости филграстима у онколошким индикацијама (50,51). Доминантност профилактичке примене дарбепоетина-алфа код тешке анемије у складу је са другим ФЕ анализама које су такође показале трошковну исплативост лечења дарбепоетином у различитим популацијама (52,53). Трошковна исплативости

профилактичке примене фондапаринукса код тешке тромбоцитопеније у складу је са другим студијама исплативости алтернативних антикоагуланаса у лечењу тромбоцитопеније узроковане применом лекова (54,55). Робусност сва три ФЕ модела потврђена је анализама сензитивности, при чему нето новчани бенефит остаје позитиван и при екстремним варирањима улазних параметара. Ово је прва студија у Србији која комбинује резултате микротрошковне студије из реалног окружења са ФЕ моделовањем за ову популацију пацијената (56), а добијени резултати представљају конкретан аргумент за доносиоце одлука у Србији да размотре финансирање ових профилактичких стратегија кроз механизме РФЗО-а (57), иако је реч о тренутно *off-label* примени лекова у датим индикацијама (58).

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4. ОБЈАВЉЕНИ И САОПШТЕНИ РЕЗУЛТАТИ КОЈИ ЧИНЕ САСТАВНИ ДЕО ДОКТОРСКЕ ДИСЕРТАЦИЈЕ

Радови објављени у водећим међународним часописима (М21а):

Stević I, Janković SM, Mihailović M, Jović I, Odalović M, Marinković V, Lakić D. Cytopenias as Adverse Drug Reactions: A 10-Year Analysis of Reporting Structure, Rate, and Trend. Pharmaceuticals (Basel). 2025 Dec 20;19(1):14. doi: 10.3390/ph19010014.

Назив часописа: Pharmaceuticals

Област: Pharmacology & Pharmacy

Импакт фактор: IF2 (2024) = 4,8 (51/352); IF5 (2024) = 4,9 (58/344)

Радови објављени у водећим међународним часописима (М21):

Stević I, Janković SM, Georgiev AM, Marinković V, Lakić D. Factors associated with hematological adverse reactions of drugs authorized via the centralized procedure. Sci Rep. 2024 Apr 20;14(1):9074. doi: 10.1038/s41598-024-59710-3.

Назив часописа: Scientific Reports

Област: Multidisciplinary sciences

Импакт фактор: IF2 (2024) = 3,9 (25/136); IF5 (2024) = 4,3 (25/135)

Радови објављени у међународним часописима (М22):

Stević I, Janković SM, Petrović N, Čanak-Baltić N, Marinković V, Lakić D. Nonchemotherapy drug-induced cytopenias: A cost-of-illness study using the microcosting methodology based on real-world data. Br J Clin Pharmacol. 2025 Jun 11. doi: 10.1002/bcp.70122. Epub ahead of print.

Назив часописа: British Journal of Clinical Pharmacology

Област: Pharmacology & Pharmacy

Импакт фактор: IF2 (2024) = 3,0 (138/352); IF5 (2024) = 3,4 (129/344)

5. ЗАКЉУЧАК – ОБРАЗЛОЖЕЊЕ НАУЧНОГ ДОПРИНОСА ДОКТОРСКЕ ДИСЕРТАЦИЈЕ

На основу детаљне анализе приложене докторске дисертације, чланови Комисије закључују да приказани резултати, дискусија и закључци представљају значајан допринос у области истраживања фармакоепидемиолошких и фармакоекономских аспеката цитопенија узрокованих применом лекова: идентификацији регулаторних фактора повезаних са очекиваним хематолошким НРЛ (укључујући цитопеније), анализи пријављивања цитопенија у клиничкој пракси на глобалном нивоу и у Републици Србији, квантификацији трошкова лечења цитопенија узрокованих применом лекова који не

припадају групи антиканцерских лекова, као и фармакоекономској евалуацији стратегија лечења ових НРЛ.

Досадашња истраживања у овој области фокусирала су се на поједине лекове или одређене терапијске групе, без свеобухватне анализе свих лекова одобрених централизованим поступком од стране Европске агенције за лекове. До сада нико није систематски испитивао повезаност регулаторних фактора са учесталошћу очекиваних цитопенија узрокованих применом лекова, нити је приказао структуру пријављивања ових НРЛ на нивоу света и појединачне земље (Република Србија), као и њихово поређење на глобалном нивоу и у Републици Србији. У Републици Србији до сада нису спровођена истраживања о директним и индиректним трошковима цитопенија узрокованих применом лекова који не припадају групи антиканцерских лекова применом методологије микротрошкова, нити фармакоекономске евалуације стратегија лечења ових стања.

Резултати истраживања показали су да значајан удео лекова одобрених централизованим поступком носи ризик од очекиване појаве ових НРЛ, при чему одређени регулаторни фактори повећавају – биосимилар, условна дозвола, присуство лека на листи есенцијалних лекова СЗО, а да је пут примене лека једини идентификовани протективни фактор. Утврђено је да су цитопеније узроковане применом лекова недовољно препознате и пријављиване у клиничкој пракси, и у свету и у Србији, да се чешће пријављују код особа женског пола, као и да потпуна информација о потреби праћења крвне слике недостаје у сажетку карактеристика лека у значајном уделу лекова који имају дозволу за лек у Србији. Трошкови лечења цитопенија узрокованих применом лекова који не припадају групи антиканцерских лекова у Србији су значајни – достижу и до 18,2% бруто домаћег производа по глави становника по случају цитопеније, а индиректни трошкови по послодавцу вишеструко су већи од индиректних трошкова које сноси РФЗО. Фармакоекономска евалуација је показала да профилактичка примена филграстима, дарбепоетина-алфа и фондапаринукс-натријума представља доминантну стратегију у поређењу са стандардном терапијом, са позитивним нето новчаним бенефитом, а робустност ових резултата је потврђена анализом сензитивности.
Подаци представљени у овој докторској дисертацији дају оригинални допринос бољем разумевању фармакоепидемиолошких и фармакоекономских аспеката цитопенија узрокованих применом лекова. Значајан научни допринос представља и примена различитих методологија која се у потпуности ослања на јавно доступне податке у анализи регулаторних фактора, као и примена микротрошковног приступа „одоздо ка горе" као златног стандарда за студије трошкова. Методологија за студију трошкова из ове докторске дисертације може да послужи као основа за будућа истраживања у Европи и свету. Добијени резултати такође указују на потребу за едукацијом здравствених радника у препознавању и пријављивању нежељених реакција овог типа, за унапређењем сажетака карактеристика лека у делу који се односи на праћење крвне слике, за проширивањем

улоге фармацеута у мониторингу терапије и омогућавања приступа лабораторијским вредностима резултата пацијената, као и за разматрањем финансирања трошковно исплативих стратегија кроз механизме Републичког фонда за здравствено осигурање.

5.1 ОЦЕНА ИЗВЕШТАЈА О ПРОВЕРИ ОРИГИНАЛНОСТИ ДОКТОРСКЕ ДИСЕРТАЦИЈЕ

На основу извештаја о провери оригиналности докторске дисертације Иване Ј. Стевић, под насловом: **„Фармакоепидемиолошки и фармакоекономски аспекти цитопенија узрокованих применом лекова“**, коришћењем програма *iThenticate* утврђено подударање текста износи 4%. Овај степен подударности последица је цитата, библиографских података о коришћеној литератури, општих места и података, као и претходно публикованих резултата докторандових истраживања, који су проистекли из његове дисертације, што је у складу са чланом 9. Правилника о поступку провере оригиналности докторских дисертација које се бране на Универзитету у Београду.

Сходно томе, може се извести закључак да је приложена докторска дисертација кандидата Иване Ј. Стевић оригинално научно дело.

6. МИШЉЕЊЕ И ПРЕДЛОГ КОМИСИЈЕ

На основу изложеног, Комисија закључује да је докторска дисертација кандидата маг. фарм. спец. Иване Стевић, чија је израда одобрена на седници Већа научних области медицинских наука Универзитета у Београду (одлука бр 61206-270/2-25 од 28.01.2025), урађена према одобреној пријави и задовољава критеријуме оригиналног научног дела. Кандидат је успешно реализовао постављене циљеве истраживања, а резултати приказани у овој докторској дисертацији представљају оригинално и самостално научно дело са значајним научним доприносом у области социјалне фармације и фармацеутске праксе. **Резултати докторске дисертације су публиковани у три рада, од тога два рада у водећим међународним часописима (М21а, М21) и један рад у међународном часопису (М22)**.

Комисија у наведеном саставу позитивно оцењује докторску дисертацију маг. фарм. спец. **Иване Стевић** под насловом: **„Фармакоепидемиолошки и фармакоекономски аспекти цитопенија узрокованих применом лекова“** и предлаже Наставно-научном већу Фармацеутског факултета, Универзитета у Београду да прихвати овај Извештај о израђеној докторској дисертацији и упути га Већу научних области медицинских наука ради добијања сагласности за јавну одбрану докторске дисертације.

07.05.2026. год.

Комисија за оцену и одбрану докторске дисертације

_____

Др сц. Душанка Крајновић
редовни професор, Универзитет у Београду - Фармацеутски факултет, председник Комисије

_____

Др сц. Слободан Јанковић,
редовни професор, Универзитет у Крагујевцу – Факултет медицинских наука

_____

Др сц. Марина Одаловић
редовни професор, Универзитет у Београду - Фармацеутски факултет

ОЦЕНА ИЗВЕШТАЈА О ПРОВЕРИ ОРИГИНАЛНОСТИ ДОКТОРСКЕ ДИСЕРТАЦИЈЕ

На основу Правилника о поступку провере оригиналности докторских дисертација које се бране на Универзитету у Београду и налаза у извештају из програма iThenticate којим је извршена провера оригиналности докторске дисертације ,,Фармакоепидемиолошки и фармакоекономски аспекти цитопенија узрокованих применом лекова", аутора Иване Ј. Стевић, констатујем да утврђено подударање текста износи 4%. Овај степен подударности последица је цитата, библиографских података о коришћеној литератури, општих места и података, као и претходно публикованих резултата докторандових истраживања, који су проистекли из његове дисертације, што је у складу са чланом 9. Правилника.

На основу свега изнетог, а у складу са чланом 8. став 2. Правилника о поступку провере оригиналности докторских дисертација које се бране на Универзитету у Београду, изјављујем да извештај указује на оригиналност докторске дисертације, те се прописани поступак припреме за њену одбрану може наставити.

06. мај 2026. године

Ментори:

Проф. др Драгана Лакић

Проф. др Валентина Маринковић

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Factors associated with hematological adverse reactions of drugs authorized via the centralized procedure

Ivana Stević[1]✉, Slobodan M. Janković[2], Andrijana Milošević Georgiev[1], Valentina Marinković[1] & Dragana Lakić[1]

Serious hematological adverse drug reactions (HADRs) may lead to or prolong hospitalization and even cause death. The aim of this study was to determine the regulatory factors associated with HADRs caused by drugs that were authorized up to July 2023 by the European Medicines Agency (EMA) and to evaluate the frequency of HADRs. Using a cross-sectional approach, the type and frequency of HADRs were collected from the Summaries of Product Characteristics of Drugs Authorized by the EMA and analyzed within proprietary, nonproprietary, and biosimilar/biological frameworks. Multivariate statistical analysis was used to investigate the associations of generic status, biosimilar status, conditional approval, exceptional circumstances, accelerated assessment, orphan drug status, years on the market, administration route, and inclusion on the Essential Medicines List (EML) with HADRs. In total, 54.78% of proprietary drugs were associated with HADRs at any frequency, while anemia, leucopenia, and thrombocytopenia were observed in approximately 36% of the patients. The predictors of any HADR, anemia, and thrombocytopenia of any frequency are generic status, biosimilar status, and inclusion on the EML, while the only protective factor is the administration route. Biosimilars and their originator biologicals have similar frequencies of HADRs; the only exception is somatropin. Knowledge of the regulatory factors associated with HADRs could help clinicians address monitoring issues when new drugs are introduced for the treatment of patients.

Keywords Hematological adverse drug reaction, Regulatory factors, Centralized procedure

An adverse drug reaction (ADR) is defined as "a response to a medicinal product which is noxious and unintended"; when considering ADRs, a causal relationship to a drug is at least a reasonable possibility[1]. If hematological adverse drug reactions (HADRs) are not a consequence of the main mechanism of action of a drug (A-type ADRs), they are unexpected ADRs (i.e., B-type ADRs)[2]. However, regardless of the mechanism of action, HADRs are usually severe, leading to hospitalization or prolonged hospitalization. A single cell line (e.g., anemia), multiple cell lines, or all bone marrow cell lines (e.g., pancytopenia) could be affected, leading to varying severity in terms of the patient's condition, prolonged hospitalization, and potentially death. Although the prevalence of HADRs is expected to increase with the use of chemotherapeutics—which directly block the multiplication of cells with a short lifecycle (e.g., the prevalence of anemia varies between 30 and 85%)—HADRs associated with nonchemotherapeutics are different, as they affect bone marrow cell lines and blood cells themselves through a variety of mechanisms, which have not been sufficiently studied[3–7].

It is estimated that ADRs account for 0.9–7.9% of hospitalizations and are the fifth most common cause of death[8,9]. One study showed that 9.01% (4/44) of ADR-related hospital admissions were due to hematological disorders, while another study reported a rate of 26.5%; however, there are no precise data in the literature on the overall frequency of HADRs[8,10]. The true prevalence of ADRs to nonchemotherapeutics can only be established after the drug is granted marketing authorization (MA) and is used for many years. As a rule, ADRs are not reported during clinical trials in the preregistration phase due to the very low incidence of adverse effects (AEs) within clinical development programs[11,12]. As a drug is on the market for a longer period of time, postmarketing surveillance is performed, including but not limited to postauthorization safety studies (PASSs), spontaneous reports, or monitoring real-world data; furthermore, the drug's Summary of Product Characteristics (SmPC)

[1]Faculty of Pharmacy, University of Belgrade, Belgrade, Serbia. [2]Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia. ✉email: ivana.stevic@pharmacy.bg.ac.rs

is updated with new data on all ADRs, including HADRs[11,13]. Therefore, as a rule, it is more risky to use drugs that are relatively new on the market in clinical practice. Drugs authorized via centralized procedures by the European Medicines Agency (EMA) are, in most cases, innovative drugs, orphan drugs, biosimilars, drugs with conditional approval, or other drugs that have been on the market for a short amount of time[14]. To help clinicians grasp the risks of HADRs when using some of the drugs authorized by the EMA, it would be useful to classify all these drugs by the degree of risk of HADRs.

Therefore, the present study aimed to evaluate the frequency of HADRs among drugs authorized through a centralized procedure and to determine the regulatory factors associated with HADRs.

Methods

The study used a cross-sectional design. The units of observation were drugs authorized for human use by the centralized procedure in the European Union (EU). Three datasets were created: (1) brand (trade)-name drugs, (2) international nonproprietary name (INN) drugs, and (3) biosimilars and their originator biologicals (hereafter referred to as biologicals). These three datasets were considered separately because ADRs are mostly reported for INN drugs, while for biologicals and biosimilars, ADR reporting also demands trade names[11]. Considering that most drugs are prescribed by trade name in clinical practice, we performed an analysis at this level, including all authorized MAs for all drugs. Initially, the EMA table of all European Public Assessment Reports (EPARs) on all drugs authorized via centralized procedures were downloaded, with a cutoff date of 30 June 2023[15]. This table provides regulatory data on drug category, trade/brand name, therapeutic area, INN, active substance, MA number, authorization status, ATC code, whether a product is additionally monitored, whether it is generic or biosimilar, whether it has conditional approval or not, whether it is authorized in exceptional circumstances via accelerated assessment, whether it is an orphan drug, MA date, MA holder, pharmacotherapeutic group, and condition/indication.

Additionally, in our datasets, we added information on the administration route and whether drugs were on the World Health Organization (WHO) Essential Medicines List (EML)[16,17]. The detailed workflow is provided in Fig. 1. For all included drugs, the HADR data were taken from part 4.8 of the SmPC, considering not only the HADR type but also its frequency.

The incidence of any HADRs, anemia, leucopenia, and thrombocytopenia were considered dependent variables or outcomes of this study. The independent variables for the purpose of this study were additional monitoring, generic status, biosimilar status, conditional approval, exceptional circumstances, accelerated assessment, orphan drug, years on the market (calculated from authorization date until dataset cutoff date), route of administration, and WHO EML.

The data were initially analyzed descriptively using rates and percentages. Then, multivariate binary logistic regression was used to reveal independent variables associated with the study outcomes. The regression models were built using the backward conditional deletion method, and the quality of the final models was verified by the Hosmer and Lemeshow test, Cox & Snell R^2, and Nagelkerke's R^2. The TREE procedure creates a tree-based model. It classifies cases into groups or predicts values of a dependent variable based on values of predictor variables. The procedure provides validation tools for exploratory and confirmatory classification analysis. Significant predictors identified by logistic regression were then used to create decision tree models that classify drugs according to the risk for HADR by creating decision rules.

The results were considered statistically significant if the probability of the null hypothesis was 0.05 or less. The statistical analysis was conducted using IBM SPSS v.29[18].

Results

The initial number of MAs in the EMA dataset was 2008. After the exclusion of veterinary drugs (n = 282) and unauthorized (withdrawn, refused) drugs (n = 377), the number of valid MAs for human use included in the statistical analysis was 1349, with 883 unique INNs. When the HADR frequency differed for the same INN (e.g., for different trade names or administration routes), both values were included. The average time from MA approval until study onset for drugs authorized by the EMA was 9.91 ± 6.97 years (0.07–27.93, median 6.96), while for biosimilars and their biologicals, it was 6.01 and 19.08 years, respectively.

In the following sections, we provide detailed results for MA, INN, biosimilars, and their biologicals.

Analysis of brand-name drugs

Almost the same number of drugs are administered enterally (47.52%) or parenterally (47.59%), while the number of locally administered drugs is much lower (3.19%). One-quarter of all MAs were under additional monitoring, with HADR occurring at any frequency in 47.63% of cases, and at least 30% of cases were anemia, leucopenia, or thrombocytopenia. One-fifth of the drugs were either generic or biosimilar, while one-tenth of the centrally authorized drugs were intended to treat rare diseases. Almost 30% of all MAs were on the WHO EML. Approximately 3% of all MAs were authorized under conditional approval, exceptional circumstances, or through an accelerated procedure.

More than half of the drugs (54.78%) were associated with HADRs, while anemia, thrombocytopenia, and leucopenia were detected in 40.47%, 41.14%, and 36.17% of cases, respectively. One-fifth of the drugs were associated with a very common frequency of any HADR (20.61%), and 15% of the MAs were associated with a very common frequency of anemia or leucopenia. One-fifth of the drugs on the EML were associated with HADRs; a total of 7.19% of the drugs were associated with a very common frequency of HADRs, and 5–6% of the drugs were associated with anemia, leucopenia, or thrombocytopenia.

Details for any or very common frequencies of HADR and their predictors are presented in Table 1.

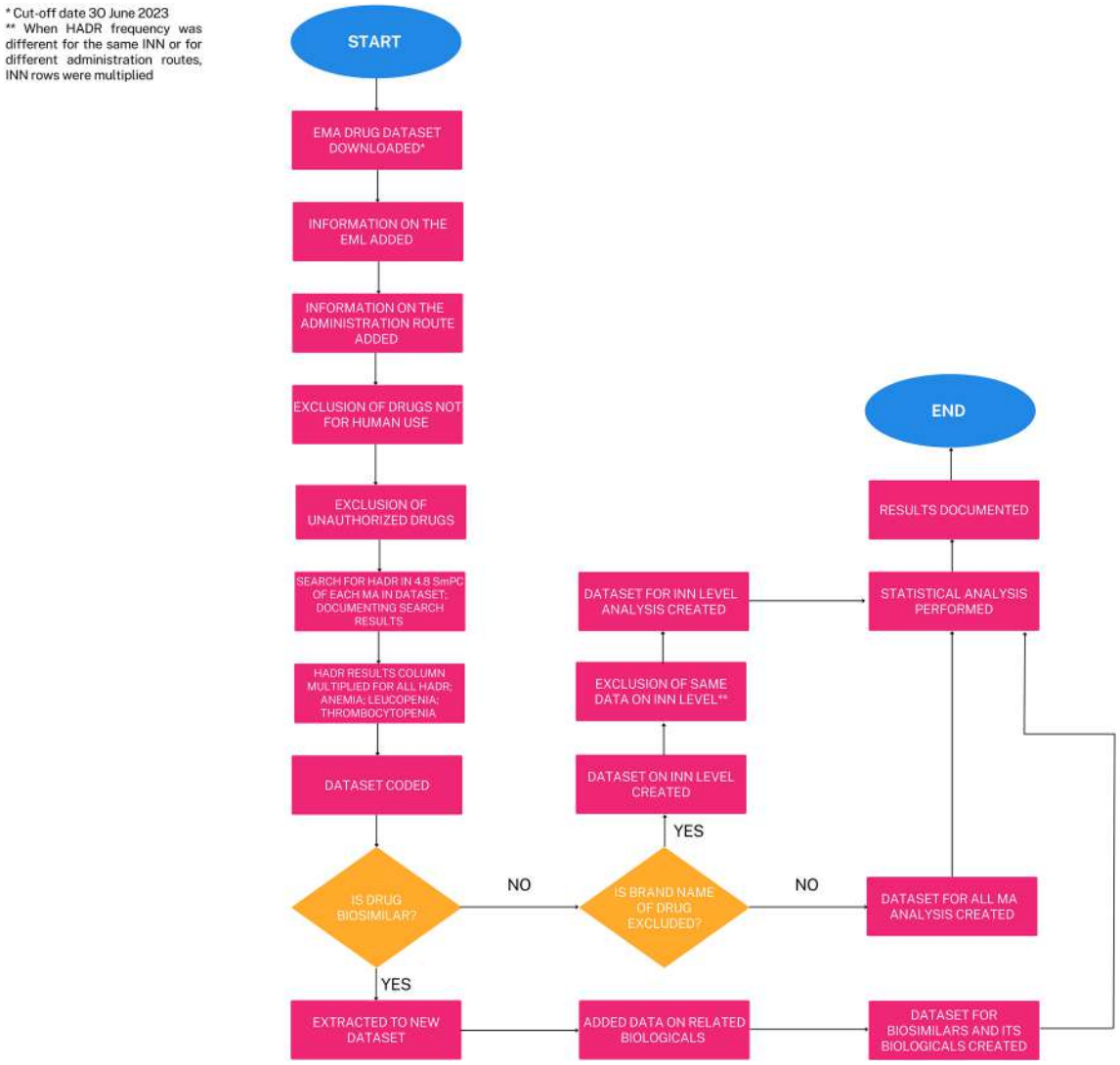

Figure 1. Workflow diagram. EMA, European Medicines Agency; EML, World Health Organization Essential Medicines List; HADR, Hematological adverse drug reaction; INN, International nonproprietary name; MA, Marketing Authorization.

Two-thirds of all MAs were found in the four ATC groups from the 1st level: A—alimentary tract and metabolism (12.38%), J—antiinfectives for systemic use (14.31%), L—antineoplastic and immunomodulating agents (29.13%), and N—nervous system (11.12%). Drugs from the L group had the highest frequency of drugs requiring additional monitoring (39.64%), generics (29.74%), biosimilars (69.74%), conditionally approved drugs (59.52%), accelerated assessment drugs (36.11%), orphan drugs (34.93%), and EML drugs (33.33%). The A group had the highest number of MAs issued under exceptional circumstances (35.14%).

All members of the P (antiparasitic products, insecticides, and repellents) group of drugs had any HADR or anemia. The L group had the highest frequency of the following HADRs: any frequency of leucopenia (74.81%); any frequency of thrombocytopenia (74.05%); very common frequency of any HADR (60.81%), anemia (46.06%), leucopenia (51.65%), and thrombocytopenia (40.71%). More detailed data about the HADRs according to ATC group can be found in the *Supplementary File*.

Multivariate binary logistic regression revealed that the following regulatory factors increased the odds of any frequency of HADR, anemia, or thrombocytopenia: generic status (odds ratio [OR] 1.76–2.37), biosimilar status (OR 3.26–11.25) and WHO EML status (OR 2.08–2.53). In the case of any frequency of leucopenia, generic status and WHO EML increased the risk by at least two times (OR 2.10 and 2.34, respectively). The only protective factor that decreased the risk of any frequency of anemia by approximately 20% was the route of administration (from highest risk to lowest risk: enteral, parenteral and local routes of administration).

A very common frequency of any HADR, anemia, leucopenia, or thrombocytopenia was increasingly reported among biosimilars, drugs with conditional approval, or drugs listed at the WHO EML. Only very common thrombocytopenia had 3 additional regulatory predictors of increased risk: generic status (OR 1.67), accelerated assessment (OR 3.03), and orphan drug status (OR 1.93). No regulatory predictor was shown to decrease the risk in the case of the very common frequency of HADRs.

Authorized drugs for human use	Number of MA	Route of administration* N (%)				Additional monitoring N (%)	Generic N (%)	Biosimilar N (%)	Conditional approval N (%)	Exceptional circumstances N (%)	Accelerated assessment N (%)	Orphan medicine N (%)	EML 2023 N (%)
		Enteral	Parenteral	Local	Enteral and parenteral								
Frequency and type of HADR	1349 (100.00)	641 (47.52)	642 (47.59)	43 (3.19)	23 (1.70)	338 (25.06)	232 (17.20)	76 (5.63)	42 (3.11)	37 (2.74)	36 (2.67)	146 (10.82)	387 (28.69)
any frequency of any HADR	739 (54.78)	368 (57.41)	349 (54.36)	5 (11.63)	17 (73.91)	161 (47.63)	166 (71.55)	66 (86.84)	22 (52.38)	12 (32.43)	16 (44.44)	68 (46.58)	278 (71.83)
very common frequency of any HADR	278 (20.61)	98 (15.29)	178 (27.73)	0 (0.00)	2 (8.70)	93 (27.51)	43 (18.53)	37 (48.68)	20 (47.62)	6 (16.22)	11 (30.56)	45 (30.82)	97 (25.06)
any frequency of ANEMIA	546 (40.47)	272 (42.43)	261 (40.65)	2 (4.65)	11 (47.83)	125 (36.98)	124 (53.45)	67 (88.16)	19 (45.24)	8 (21.62)	13 (36.11)	50 (34.25)	231 (59.69)
very common frequency of ANEMIA	199 (14.75)	77 (12.01)	120 (18.69)	0 (0.00)	2 (8.70)	71 (21.01)	32 (13.79)	23 (30.26)	18 (42.86)	5 (13.51)	9 (25.00)	36 (24.66)	69 (17.83)
any frequency of LEUCOPENIA	488 (36.17)	250 (39.00)	227 (35.36)	2 (4.65)	9 (39.13)	106 (31.36)	124 (53.45)	38 (50.00)	17 (40.48)	7 (18.92)	12 (33.33)	51 (34.93)	200 (51.68)
very common frequency of LEUCOPENIA	214 (15.86)	73 (11.39)	139 (21.65)	0 (0.00)	2 (8.70)	72 (21.30)	40 (17.24)	29 (38.16)	15 (35.71)	3 (8.11)	7 (19.44)	34 (23.29)	81 (20.93)
any frequency of THROMBOCY-TOPENIA	555 (41.14)	283 (44.15)	261 (40.65)	1 (2.33)	10 (43.48)	110 (32.54)	140 (60.34)	54 (71.05)	16 (38.10)	6 (16.22)	14 (38.89)	50 (34.25)	237 (61.24)
very common frequency of THROMBOCY-TOPENIA	173 (12.82)	62 (9.67)	109 (16.98)	0 (0.00)	2 (8.70)	59 (17.46)	31 (13.36)	26 (34.21)	14 (33.33)	4 (10.81)	10 (27.78)	32 (21.92)	67 (17.31)

Table 1. Characteristics of drugs for which marketing authorization was granted by the EMA. EML, World Health Organization Essential Medicines List; HADR, Hematological Adverse Drug Reaction; MA, Marketing Authorization.

Table 2 shows the regulatory factors that increased or decreased the risk of any frequency and very common frequency of any HADR or specific blood disorders analyzed in this study, as well as the features of the logistic regression model. The decision tree of having HADR with any (Fig. 2) or very common frequency (Fig. 3) was satisfactorily differentiated based on the revealed predictors. Figure 4 presents all the predictors that were analyzed.

Analysis of INNs

Characteristics of any frequency and very common frequency of HADRs, anemia, leucopenia, and thrombocytopenia at the INN level are shown in Table 3. One-fifth of INNs were listed on the WHO EML, and one-third of the INNs were under additional monitoring. Only 3.62% of the INNs were approved through the accelerated assessment, while approximately 4% of INNs were under conditional approval or exceptional circumstances. Half of the INNs had a HADR of any frequency, and one-fifth of the INNs were associated with HADRs with a very common frequency. One-third of the drugs were associated with any frequency of anemia, leucopenia, or thrombocytopenia, while 13–16% of INNs were associated with a very common frequency of these blood disorders.

The logistic regression for INNs did not reveal any factors that act protectively on the risk of any HADR of any or a very common frequency. WHO EML status was the only regulatory factor that increased the risk by approximately 1.5 times for any frequency of HADR, anemia, leucopenia, or thrombocytopenia. The factors increasing the risk of a very common frequency of any HADR and anemia were mandatory additional monitoring (ORs of 1.48 and 1.67, respectively) and conditional approval (ORs of 2.60 and 3.01, respectively). Conditional approval and orphan status increased the risk of very common leucopenia by 2.13 and 1.71 times, respectively. The risk of very common thrombocytopenia increased when a drug had conditional approval, was approved through accelerated assessment, or was an orphan drug (OR 2.70, 2.75 and 1.77, respectively).

Frequency	Hematological Adverse Drug Reaction (HADR)	Factors that increase the risk factor (OR; 95% CI; p value)	Factors that decrease the risk factor (OR; 95% CI; *p* value)	Model features Hosmer and Lemeshow Test (chi-square; df; p value) Cox & Snell R^2 Nagelkerke's R^2	Figures
ANY FREQUENCY	Any HADR	Generic (2.35; [1.65–3.34]; < 0.001) Biosimilar (5.91; [2.90–12.01]; < 0.001) EML (2.08; [1.59–2.74]; < 0.001)	–	11.56; 8; 0.172 0.09 0.12	Fig. 2A
	Anemia	Generic (1.76; [1.29–2.40]; < 0.001) Biosimilar (11.25; [5.41–23.38]; < 0.001) EML (2.32; [1.78–3.01]; < 0.001)	Route of administration (0.79; [0.65–0.96]; 0.016)	12.58; 8; 0.127 0.11 0.15	Fig. 2B
	Leucopenia	Generic (2.10; [1.50–2.94]; < 0.001) EML (2.24; [1.72–2.92]; < 0.001)	–	11.84; 8; 0.158 0.07 0.09	Fig. 2C
	Thrombocytopenia	Generic (2.37; [1.74–3.23]; < 0.001) Biosimilar (3.26; [1.89–5.64]; < 0.001) EML (2.53; [1.94–3.28]; < 0.001)	–	8.41; 5; 0.135 0.10 0.14	Fig. 2D
VERY COMMON	Any HADR	Biosimilar (3.32; [1.94–5.66]; < 0.001) Conditional approval (2.84; [1.41–5.72]; 0.004) EML (1.39; [1.01–1.92]; 0.042)	–	12.39; 8; 0.135 0.05 0.08	Fig. 3A
	Anemia	Biosimilar (2.27; [1.26–4.11]; 0.007) Conditional approval (3.41; [1.65–7.04]; < 0.001) EML (1.47; [1.02–2.11]; 0.038)	–	10.35; 8; 0.241 0.04 0.07	Fig. 3B
	Leucopenia	Biosimilar (2.73; [1.56–4.79]; < 0.001) Conditional approval (2.24; [1.07–4.72]; 0.033) EML (1.59; [1.13–2.26]; 0.009)	–	5.50; 8; 0.704 0.04 0.08	Fig. 3C
	Thrombocytopenia	Generic (1.67; [1.01–2.76]; 0.047) Biosimilar (3.85; [2.12–7.01]; < 0.001) Conditional approval (2.96; [1.36–6.44]; 0.006) Accelerated assessment (3.03; [1.35–6.81]; 0.007) Orphan medicines (1.93; [1.12–3.35]; 0.019) EML (1.57; [1.07–2.30]; 0.020)	–	14.01; 8; 0.081 0.05 0.09	Fig. 3D

Table 2. Predictors of any and very common frequency of HADR (only significant predictors are shown for the sake of clarity). EML, World Health Organization Essential Medicine List; Fig, Figure.

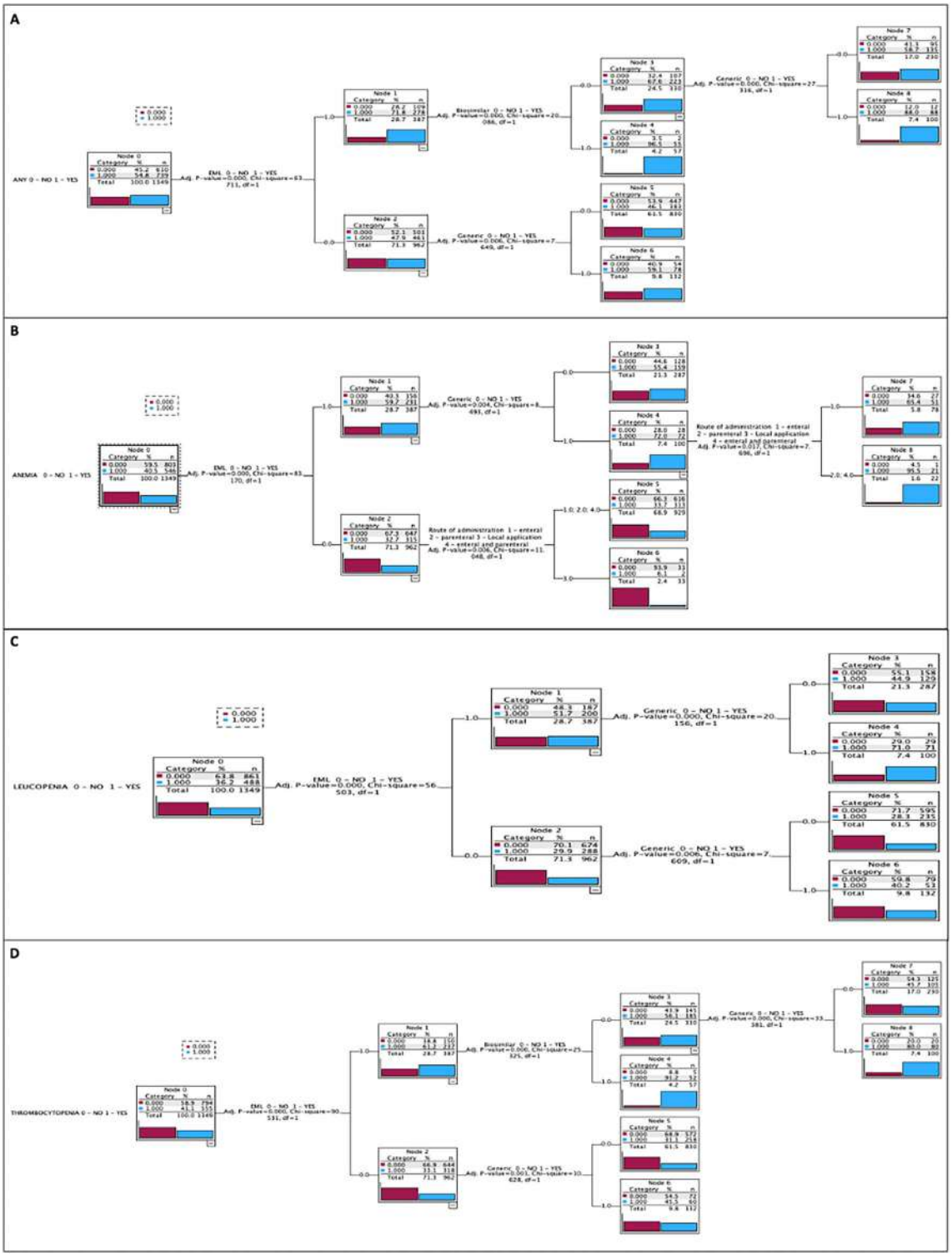

Figure 2. Decision tree showing the effects of a combination of predictors on the probability of hematological adverse drug reactions (HADRs) of any frequency. (**A**) Any HADR; (**B**) ANEMIA; (**C**) LEUCOPENIA; (**D**) THROMBOCYTOPENIA. EML, World Health Organization Essential Medicines List.

Analysis of biosimilars and related biologicals

We found 19 unique INNs within biosimilars, with 96 MAs, including their biologicals. All biosimilars were administered parenterally, where two out of three (63.16%) were under additional monitoring, and the majority were on the WHO Essential Medicine List (57.89%). No biosimilar was authorized conditionally or under exceptional circumstances. Only one item was approved via accelerated assessment, and only one item had the status of an orphan drug.

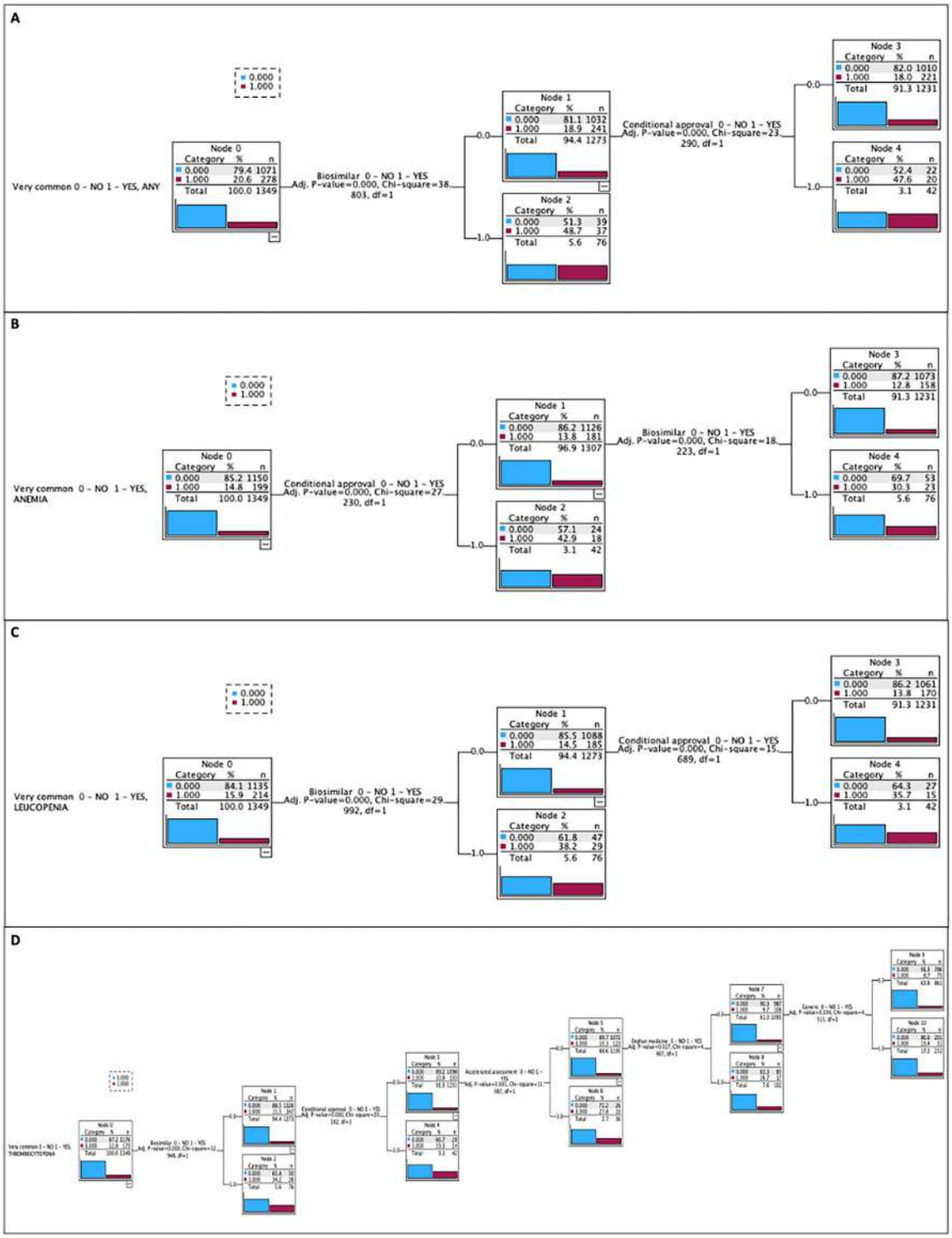

Figure 3. Decision tree showing the effects of a combination of predictors on the probability of hematological adverse drug reactions (HADRs) of very common frequency. (**A**) Any HADR; (**B**) ANEMIA; (**C**) LEUCOPENIA; (**D**) THROMBOCYTOPENIA.

No discrepancy was found in the HADR frequency among biosimilars of the same INN. Only somatropin had a difference in the frequency of HADR, whereas biosimilars had no HADR in comparison to biologicals, which have anemia with an uncommon frequency. Trastuzumab was the only INN associated with a very common frequency of anemia, leucopenia, and thrombocytopenia among the biosimilars. Four out of five authorized biologics (biosimilars + biologicals) had any frequency of HADR or anemia, while three out of four had HADR or anemia at the INN level. Leucopenia was most common (34.38% for the MA level, 21.05% for the INN level). Table 4 shows an overview of the frequencies of any or a specific HADR at the MA or INN level. The biosimilars

Figure 4. Predictors that were analyzed (red—factors significantly increasing the risk; green—factors significantly decreasing the risk; orange—factors that showed no significance). EML, World Health Organization Essential Medicine List.

Authorized drugs for human use	Total number of INN N (%)	Additional monitoring N (%)	Conditional approval N (%)	Exceptional circumstances N (%)	Accelerated assessment N (%)	Orphan medicine N (%)	EML 2023 N (%)
Frequency and type of HADR	883 (100.00)	296 (33.52)	41 (4.64)	36 (4.08)	32 (3.62)	142 (16.08)	197 (22.31)
Any frequency of any HADR	462 (52.32)	130 (43.92)	22 (53.66)	12 (33.33)	14 (43.75)	66 (46.48)	117 (59.39)
Very common frequency of any HADR	191 (21.63)	80 (27.03)	20 (48.78)	6 (16.67)	10 (31.25)	45 (31.69)	39 (19.80)
Any frequency of ANEMIA	327 (37.03)	95 (32.09)	19 (46.34)	8 (22.22)	11 (34.38)	48 (33.80)	89 (45.18)
Very common frequency of ANEMIA	140 (15.86)	65 (21.96)	18 (43.90)	5 (13.89)	8 (25.00)	36 (25.35)	25 (12.69)
Any frequency of LEUCOPENIA	298 (33.75)	90 (30.41)	17 (41.46)	7 (19.44)	10 (31.25)	49 (34.51)	80 (40.61)
Very common frequency of LEUCOPENIA	137 (15.52)	59 (19.93)	15 (36.59)	3 (8.33)	6 (18.75)	34 (23.94)	29 (14.72)
Any frequency of THROMBOCYTOPENIA	320 (36.24)	86 (29.05)	16 (39.02)	6 (16.67)	12 (37.50)	48 (33.80)	87 (44.16)
Very common frequency of THROMBOCYTOPENIA	114 (12.91)	65 (21.96)	14 (34.15)	4 (11.11)	9 (28.13)	32 (22.54)	22 (11.17)

Table 3. Characteristics of INNs authorized by the EMA. EML, World Health Organization Essential Medicine List; HADR, Hematological Adverse Drug Reaction; INN, International Nonproprietary Name.

were found only in six ATC groups (A, B, G, H, L, and S). In the *Supplementary File,* the results of any or specific HADR for biosimilars and their biologicals for all frequencies per ATC group are presented.

In the *Supplementary File*, the checklist is provided, listing all INNs with their respective brand names according to the frequency of anemia, leucopenia, and thrombocytopenia, taking into account only very common occurrences.

Discussion

Our results showed that any HADR of any frequency was detected in approximately 55% of all MAs; this frequency was greater for drugs with a generic status or biosimilar status or for those listed in the WHO EML. The risk of very common HADRs was significantly increased among drugs with biosimilar status, drugs included on the WHO EML, and drugs with conditional MA.

BIOSIMILARS		Very common N (%)	Common N (%)	Uncommon N (%)	Rare N (%)	Very rare N (%)	Not known N (%)	Any frequency N (%)
INN level	ANY HADR	6 (31.58)	10 (52.63)	7 (36.84)	8 (42.11)	2 (10.53)	3 (15.79)	14 (73.68)
	ANEMIA	3 (15.79)	7 (36.84)	3 (15.79)	7 (36.84)	1 (5.26)	0 (0.00)	14 (73.68)
	LEUCOPENIA	4 (21.05)	4 (21.05)	3 (15.79)	3 (15.79)	0 (0.00)	1 (5.26)	7 (36.84)
	THROMBOCYTOPENIA	4 (21.05)	4 (21.05)	4 (21.05)	4 (21.05)	0 (0.00)	1 (5.26)	10 (52.63)
MA level	ANY HADR	41 (42.71)	61 (63.54)	46 (47.92)	36 (37.50)	10 (10.42)	17 (17.71)	78 (81.25)
	ANEMIA	25 (26.04)	35 (36.46)	20 (20.83)	35 (36.46)	4 (4.17)	0 (0.00)	79 (82.29)
	LEUCOPENIA	33 (34.38)	23 (23.96)	12 (12.50)	20 (20.83)	0 (0.00)	6 (6.25)	45 (46.88)
	THROMBOCYTOPENIA	29 (30.21)	27 (28.13)	23 (23.96)	21 (21.88)	0 (0.00)	7 (7.29)	62 (64.58)

Table 4. HADR frequency of biosimilars and their biologicals authorized by the EMA. HADR, Hematological Adverse Drug Reaction; INN, International Nonproprietary Name; MA, Marketing Authorization.

Our analysis at the level of the INN showed that no factor exerted significant protective effects against all or specific HADRs of any frequency, while WHO EML was a factor that increased the risk of any frequency of all analyzed HADRs.

The majority of the factors associated with HADRs increase the risk (e.g., generic status, biosimilar, WHO EML, conditional approval, additional monitoring, etc.), while only the administration route was a protective factor.

In patients taking biosimilars and their biological drugs, HADRs are very common. Bearing in mind that until recently, i.e., until the position of the EMA in September 2022[19], biosimilars and biological drugs were not considered mutually interchangeable, as is the case with generic drugs and their reference; therefore, the transition in therapy from one to another biological or biosimilar was not common. Our results showed that there was no difference in the frequency of hematological reactions between biosimilars and their reference biological drug, which is in line with other studies[11], except in the case of somatropin, where the biosimilar does not have anemia with an unknown frequency listed as HADR while the reference drug does.

For a drug, generic or biosimilar, to be marketed, the data exclusivity of the reference drug must expire so that the drug first receives marketing authorization from the regulatory body and then that the market protection of the reference drug expires for the generic or biosimilar drug to be placed on the market[20,21]. This takes tens of years, depending on the regulations, and during that time, the reference drug is also undergoing postmarketing monitoring. These factors are expected to impact the frequency of HADRs because more real-world data on the type of ADR and its frequency, where generics and biosimilars are marketed, are available, and active substances are being monitored for a more extended period.

The influence of the inclusion of a drug on the WHO EML as a factor can be explained by the requirements that must be met for the drug to be considered for the EML, such as evidence on comparative effectiveness, safety, costs, cost-effectiveness, regulatory status, market availability, and others[22]. To fulfill all the previously mentioned requirements, the drug must be on the market and an active substance used for many years, leading to the well-known safety profile of this drug.

Conditional MA status implies continuous monitoring of the use of the drug (most often, the continuation of clinical trials or mandatory PASSs) and, therefore, highly monitored reporting of ADRs. Studies have shown no increased risk of safety issues for conditionally approved drugs[23].

Additional monitoring is a factor that increases the risk, which is required when more data on drug safety or efficacy are needed to evaluate the benefit-risk profile worldwide considering long-term use, whether the drug is a new active substance or biological drug, whether it has conditional approval, whether it is approved under exceptional circumstances, or when the MA holder must conduct additional studies or be approved with special obligations[24]. For these drugs to be closely monitored, more pharmacovigilance activities and more real-world data are expected, explaining our study's results[23].

The orphan status of a drug is also shown to increase the risk of HADR. Considering the rarity and severity of diseases in which patients are treated with these drugs (life-threatening or chronically debilitating), close monitoring of patients receiving orphan drugs is expected, especially given the large amount of data related to ADRs, which may influence the change in the safety profile of drugs for SmPC[25]. One study showed that 70% of drugs authorized by the FDA had changes in labeling due to safety[26].

Accelerated assessment is used by the EMA when drug approval in shorter review timelines is considered to be of major public health interest or represents a therapeutic innovation[27]. The justification that a drug fulfills one of these conditions is left to the applicant without a clear definition of a major public health interest[28]. Our study showed that accelerated assessment increases the risk of HADR, which is in line with other studies showing the potential relationship between 'fast track' or 'priority review' and postapproval safety issues[23].

The influence of the administration route on HADRs was also shown in a study conducted by Ingrasciotta et al., where red cell aplasia was linked to the route of administration in the case of epoetin alfa[11].

Study limitations

The main limitation of this study was that only drugs authorized through centralized procedures were analyzed. However, this factor was not expected to have a significant impact since the majority of novel drugs are authorized

by the EMA. Additional studies analyzing drugs authorized through national procedures (NPs), decentralized procedures (DPs), or mutual recognition procedures (MPRs) are necessary. More drugs are approved through NPs, DPs, and MRPs than through the CP, but drugs authorized by the EMA are available for fewer years on the market (our study showed that half of them have been available for less than 7 years since authorization, which does not mean that they were on the market from the first day), leading to insufficient awareness of the HADR of these drugs. Additionally, we did not consider possible differences in the SmPC between the EMA and other medical agencies, e.g., the Food and Drug Administration (FDA), even though it is known that there may be discrepancies in product information and differences in the decision-making regulatory framework between these two regulators[29–31] and different safety conclusions between the EU and Canada and the United Kingdom (UK)[32].

Additionally, we did not perform a statistical analysis in which the predictor was the therapeutic group or drug indication.

Strengths of the study

To the best of our knowledge, this is the first study investigating the association between regulatory factors and HADRs and the first study using a methodology that completely relies on publicly available data. Ferner et al. explored data available in the SmPC related to monitoring for HADR using the UK's electronic database[33]. The main strength of our study was that we included all drugs authorized through the CP without therapeutic limitations or authorization date limitations, which was not the case in other studies using the EMA database as the main source of data. Mol et al. excluded biosimilars when conducting a study related to postapproval safety issues with innovative drugs[23]; Francisca RDC et al. analyzed drugs authorized between 2006 and 2017, excluding generics, when analyzing the introduction or discontinuation of additional risk minimization measures (RMMs)[32]; Zeitoun et al. explored the association between regulatory review time and postmarket safety events excluding reformulations, combination therapies, nontherapeutic agents, generics and biosimilars with limitations on authorization dates (2001–2010)[34]; and Meregaglia et al. excluded drugs receiving MA before 2017 when assessing patient-reported outcomes in the authorization by the EMA[31]. We analyzed SmPC data from each of the 1349 authorized MAs for drugs for human use since SmPC is considered a routine RMM, and one study showed that 36% of additional RMMs targeted "blood and blood-forming organs"[31].

We also added and analyzed the impact of the administration route as well as the presence of a drug on the WHO EML. The additional strength of the study is that it analyzed the HADRs for each MA, INN, and biosimilar and their biological agents.

Conclusion

There are certain characteristics of drugs that are associated with hematological adverse reactions; they reflect the idiosyncratic nature of the majority of hematological adverse reactions, which require time and widespread use to be recognized a sufficient number of times and then entered the official summary of product characteristics. Knowledge of these characteristics could be of use to clinicians when choosing a drug that should be prescribed to a patient prone to anemia, leucopenia or thrombocytopenia, as well as when an observed hematological adverse reaction should be ascribed to one of numerous drugs the patient was taking simultaneously.

Data availability

The data used in the study and other materials not contained in the Supplementary File are available to interested readers from the corresponding author upon reasonable request.

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Author contributions

I.S.—conceptualization, methodology, software, formal analysis, data curation, writing—original draft preparation, visualization, investigation, validation, writing—reviewing and editing. S.M.J.—conceptualization, methodology, software, formal analysis, data curation, writing—original draft preparation, visualization, investigation, supervision, validation, writing—reviewing and editing. A.M.G.—data curation, writing—original draft preparation, writing—reviewing and editing, funding acquisition. V.M.—data curation, writing—original draft preparation, writing—reviewing and editing, funding acquisition. D.L.—conceptualization, methodology, software, formal analysis, data curation, writing—original draft preparation, visualization, investigation, supervision, validation, writing—reviewing and editing.

Competing interests

The authors declare no competing interests.

Additional information

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Correspondence and requests for materials should be addressed to I.S.

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ORIGINAL ARTICLE

Nonchemotherapy drug-induced cytopenias: A cost-of-illness study using the microcosting methodology based on real-world data

Ivana Stević[1] | Slobodan M. Janković[2,3] | Nemanja Petrović[2,3] | Nataša Čanak-Baltić[2] | Valentina Marinković[1] | Dragana Lakić[1]

[1]University of Belgrade, Faculty of Pharmacy, Belgrade, Serbia

[2]University of Kragujevac, Faculty of Medical Sciences, Kragujevac, Serbia

[3]Department of Clinical Pharmacology, University Clinical Center of Kragujevac, Serbia

Correspondence
Ivana Stević, University of Belgrade, Faculty of Pharmacy, Belgrade, Serbia.
Email: ivana.stevic@pharmacy.bg.ac.rs

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Aims: Our study aimed to determine the healthcare utilization and costs of nonchemotherapy drug-induced cytopenias and analyse the main drivers of costs.

Methods: This cost-of-illness study was conducted using the microcosting (bottom-up) approach based on real-world data. Data on the patients who developed leucopenia, anaemia or thrombocytopenia as nonchemotherapy drug-induced blood disorders were extracted from records of the inpatients treated in a tertiary care university hospital.

Results: The study included 46, 71 and 80 cases of leucopenia, anaemia and thrombocytopenia, respectively. Leucopenia had the highest costs per case (average: 200 928.4, median: 176 078.4 Serbian dinars [RSD], interquartile range: 171 223.4 RSD), followed by thrombocytopenia (average: 115 065.2, median: 89 732.4 RSD, interquartile range: 77 755.9 RSD) and anaemia (average: 109 502.5, median: 90 267.3 RSD, interquartile range: 74 225.1 RSD). These costs expressed as Gross Domestic Product per capita based on purchasing power parity were 6.97, 2.85 and 2.84% for leucopenia, anaemia and thrombocytopenia, respectively. In leucopenia, 48.9% of the costs were the costs of drugs, while in anaemia and thrombocytopenia, the majority of the costs were due to the length of hospitalization (38.6 and 34.7%, respectively). The factors with the greatest influence on the total costs of anaemia and thrombocytopenia were the length of hospitalization and the number of computed tomography scans, while the cost of leucopenia treatment was most influenced by survival status, age and the number of laboratory tests.

Conclusions: Our study showed that the use of healthcare services and costs caused by nonchemotherapy drugs are considerable. Proactive strategies to manage and prevent drug-induced cytopenias should be considered.

KEYWORDS
cost-of-illness, drug-induced cytopenias, microcosting, real-world data

1 | INTRODUCTION

With the expansion of pharmacotherapy and increasingly frequent polypharmacy, drug-induced disorders are increasingly encountered in clinical practice. It is precisely these disorders, including haematological disorders caused by noncytostatic drugs, that pose a challenge in the real world because clinicians do not expect them.[1–4] While the prevalence of haematological adverse drug reactions

(ADRs) in chemotherapeutics is high, there is insufficient epidemiological data for nonchemotherapeutics (all drugs except cytostatics, including standard classes of drugs or targeted therapy). Although a spontaneous reporting system is mandatory during a drug's life cycle, it is estimated that around 94% of ADRs are not reported.[2–9]

One of the most common haematological conditions is a disorder in the number of blood cells (leukocytes, erythrocytes or platelets), which could be caused by the use of a drug,[1] further referred to in the text as drug-induced cytopenia (DIC). According to current data, every third registered drug via centralized procedure by the European Medicines Agency has the potential to cause either anaemia, leucopenia or thrombocytopenia.[10] Still, the frequency of occurrence in the group of patients exposed to a single drug is not high.

Frequency data on hospital admissions due to haematological ADRs vary between studies, from 9%[11] up to 26.5%.[12] When these disorders occur, their severity is often such that they can be life-threatening, requiring hospitalization or prolongation and consequently leading to cost increases in the healthcare system.[13–16] Relatively high frequency of haematological ADRs, including cytopenias, was confirmed by the systematic review of Abu *et al*., which included 12 studies of hospitalized patients (including both internal medicine and surgical patients) with varying rates from 9.9 to 15.2%.[13] In a cohort study by Geer *et al*. on 5482 patients with internal medicine disorders of a single tertiary care hospital, it was found that up to 10% of all ADRs were cytopenias.[17]

Due to its relatively rare occurrence, lack of causality with the main mechanism of action of nononcology drugs, and, therefore, more difficult recognition, the consequences caused by DICs are often neglected in pharmacoeconomic studies, which may lead to an overestimation of the cost-effectiveness of some drugs.

Hospitalization or its prolongation is often led by DICs and sometimes requires additional therapy, where the costs of treating such patients are high, but we lack their precise assessment. Most of the studies that have dealt with the costs of drug-induced disorders are based on the macro-costing principle and do not provide the details of the treatment of patients. Microcosting studies with a bottom-up approach represent the most precise methodology and the gold standard for conducting cost-of-illness (COI) studies.[18–20] While there are published studies of COI for chemotherapy-induced cytopenia, there are limited numbers of COI studies for nonchemotherapy drugs, mainly focused on heparin-induced thrombocytopenia or ribavirin-induced anaemia, where the minority are done using a microcosting approach.[21–24]

The aim of our study is to use microcosting (a bottom-up approach) to determine healthcare utilization and costs of nonchemotherapy DICs, including anaemia, leucopenia and thrombocytopenia, based on real-world data, and to analyse the main drivers of both utilization and cost outcomes.

What is already known about this subject

- The costs of treatment of chemotherapy-induced cytopenias are known, while for nonchemotherapy drug-induced cytopenias, the data are scarce and related to just a few drugs.
- Although nonchemotherapy drug-induced cytopenias are relatively frequently met in clinical practice, they are usually not understood as drug-induced, leading to an underestimation of the total treatment costs.

What this study adds

- This study estimated the precise real-world costs and healthcare utilization of treating nonchemotherapy drug-induced cytopenias (leucopenia, anaemia and thrombocytopenia).
- Healthcare utilization and costs caused by nonchemotherapy drugs are considerable and should be taken into account when assessing the cost-effectiveness of nonchemotherapy drugs.

2 | METHODS

2.1 | Type of the study

The COI study was conducted using the microcosting, bottom-up approach. The real-world data were collected at the Department of Clinical Pharmacology, University Clinical Center of Kragujevac, with the approval of their Ethics Committee (decision number: 01/22–340 from 10.10.2022). The need for informed consent was waived by the Ethics Committee due to the retrospective nature of the research. The study was conducted according to the plan available at https://farfar.pharmacy.bg.ac.rs/handle/123456789/5623.

On the patient level, retrospective data covering 3 years (1 January 2020–31 December 2022) were collected by extracting them from the archive of patient records (paper-based/electronic records of clinical pharmacologist consultations).

This retrospective COI study was conducted from the perspective of the Serbian Health Insurance Fund (HIF).

Since there is no widely accepted guideline or checklist for conducting microcosting studies, we used a consensus-based checklist proposed by a group of authors, reporting schemes from published microcosting studies, and we also considered the strengths and limitations of published systematic reviews of costing studies.[24–27]

2.2 | Research population

The study population was selected based on the following inclusion criteria: patients admitted to a tertiary care hospital, having anaemia, leucopenia or thrombocytopenia mentioned in: (i) any part of the clinical pharmacologist's report; (ii) having laboratory findings indicating these disorders; or (iii) having a diagnosis code corresponding to these disorders attached to the patient file. The patients were excluded if any of the following criteria were met: history of surgery; COVID-19; having any form of malignant disease or any other disease/disorder that in its natural course has the potential of haematological disorder (renal failure, lupus, hepatitis C, myelodysplastic syndrome, liver cirrhosis etc.); or incomplete medical record.

2.3 | Sampling

The sampling process (Figure 1) was completed through 2 phases: (i) screening and (ii) causality assessment. In the first phase, 2 independent researchers (I.S., N.Č.B.) reviewed 11 405 paper-based clinical pharmacologists' reports, which are part of patient files (1 January 2020–31 December 2022), screening for drug-induced blood disorders focusing on anaemia, leucopenia and thrombocytopenia. These disorders were screened manually by reading patient history, physician findings, laboratory findings and diagnosis codes. The number of reports fulfilling the inclusion criteria was 753. For these selected cases, patients' electronic records were screened (S.J., N.P.) for more details, and exclusion criteria were applied, leading to 217 reports qualified for the second phase.

In the second phase, an experienced clinical pharmacologist (S.J.) determined that there was enough evidence that cytopenia was a consequence of the drug administered to the patient (causal relationship between drug[s] and blood disorders categorized by the World Health Organization Uppsala Monitoring Centre system as at least *probable*) in 141 reports.[28] Some of the cases were related to the same patient at different time points, or 1 patient experienced multiple disorders (e.g., anaemia and thrombocytopenia), having leucopenia determined in 46 cases, anaemia in 71 cases and thrombocytopenia in 80 cases.

2.4 | Variables measured in the study

The study outcomes (dependent variables) extracted from the patient records were utilization data. The costs were calculated using utilization data and unit prices of healthcare services according to the HIF pricelist[29–31]:

Service costs = number of services provided × price of the service.

Drug costs = number of drug units used × price of the drug.

The levels of anaemia, leucopenia and thrombocytopenia (grade 1–5) were expressed based on laboratory values using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.[32]

Predictors of interest for which real-world data on individual patient levels were collected were: (i) demographic data: sex, age; (ii) patient status: live or dead; (iii) laboratory and diagnostic services: blood count number (haemoglobin value, number of red blood cells, number of white blood cells, platelet number), number of biochemical analyses, number of microbiological analyses, morphological diagnostic service (number of computed tomography scans [CTs], X-ray images, magnetic resonance imaging, electrocardiogram); (iv) therapeutic services: number of hospital days, healthcare professional and haematologist's consultations; (v_a) patient therapy (drug brand name number, drug International Nonproprietary Name [INN] number, number of drugs [INN] having cytopenia as ADR in the Summary of Product Characteristics); (v_b) transfusion (number of: platelet units, red blood cells, white blood cells, plasma units, blood derivates units, whole blood units, coagulation factors units).

Discounting of the costs was not considered since the HIF did not change the prices of healthcare services during the observed period. All costs are expressed in Serbian dinars (RSD).

We also present costs expressed as % of gross domestic product (GDP) per capita and % GDP per capita, as well as purchasing power parity (PPP), for international comparison purposes. In addition, in the *Appendix file*, costs are presented in US dollars (USD) and an explanation of how costs expressed in % GDP per capita, %GDP per capita, PPP and in USD were calculated is provided.

2.5 | Study power and sample size

The confidence interval for our study was 95%, where the sample size (N) for each blood disorder of interest (anaemia, leucopenia, thrombocytopenia) was calculated based on the formula[33]:

$$N = \left(\frac{2 * 1.96}{E} * SD\right)^2$$

SD (standard deviation) and E (desired margin of error) were based on data from the cost-of-illness study of Haematological Complications of Chemotherapy.[34] Expected cost standard deviations were: 28 598.3 RSD (leucopenia); 29 510.1 RSD (anaemia); 45 634.7 RSD (thrombocytopenia) with desired margin of error 20 000.0 RSD, 20 000.0 RSD, 25 000.0 RSD, respectively.

According to the formula above, a minimum number of cases per disorder was: (i) leucopenia: 31; (ii) anaemia: 33; (iii) thrombocytopenia: 51.

2.6 | Statistical data processing

The data were first tabulated and checked for accuracy. Continuous variables were described by mean, standard deviation, median and interquartile range, while categorical variables were described by rates and percentages. If the data were normally distributed, differences in the values of continuous variables among study groups were tested

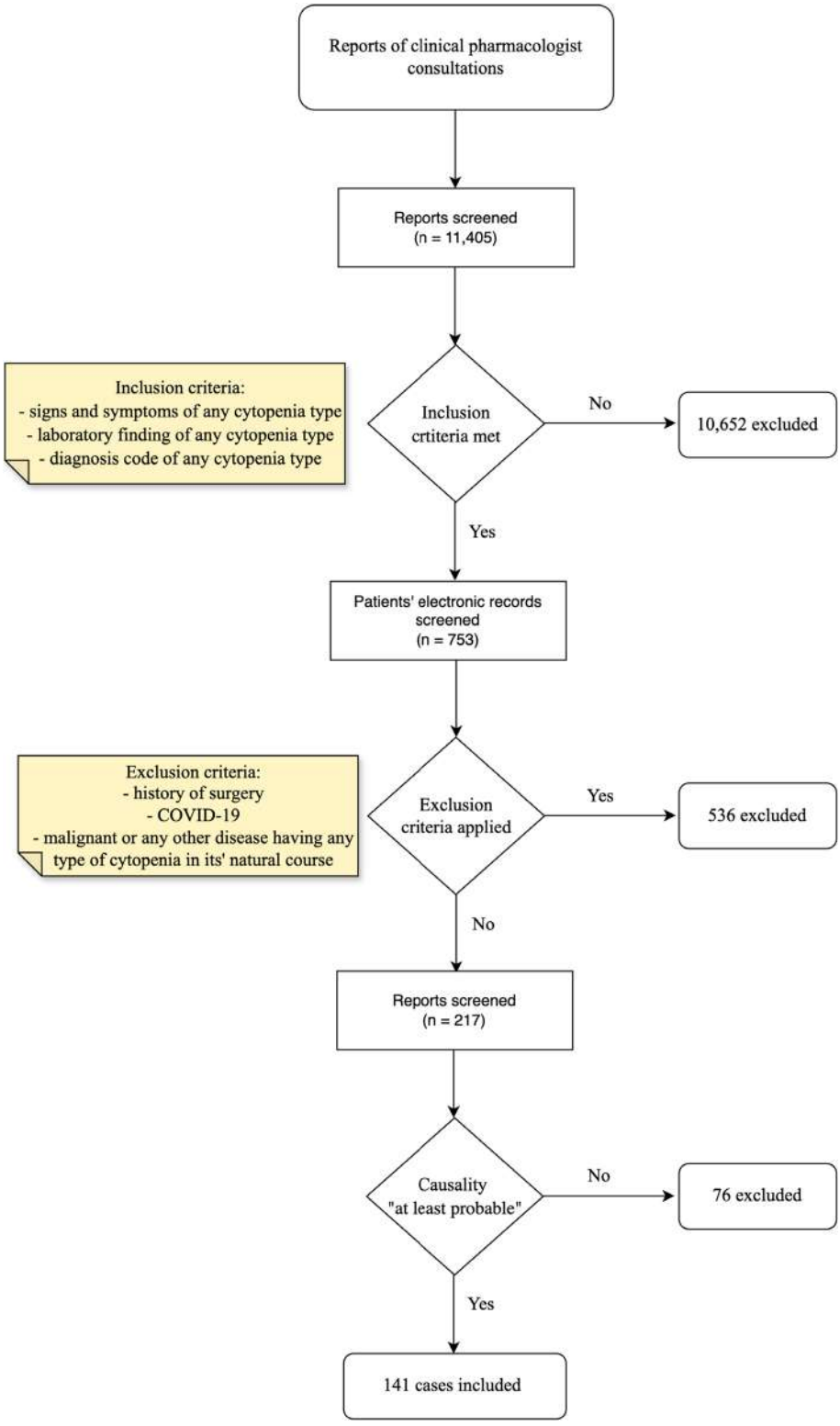

FIGURE 1 Case selection flow diagram.

by Student *t*-test or ANOVA, or, if not, by Kruskal–Wallis or Mann–Whitney *U*-test. Differences in rates or percentages of categorical variables were tested by chi-square or Fisher's exact test.

Afterward, a generalized linear model (GLM) was used for multivariate analysis to determine whether variables mentioned in the text above were associated with the study outcomes: costs. The model was built using a gamma distribution and a log link function. The goodness of fit was estimated based on deviance, chi-square statistics and Akaike information criteria (AIC). The Omnibus test was used to estimate the validity of the model.

The results were considered statistically significant with the null hypothesis probability being ≤.05. IBM SPSS v. 29[35] and Microsoft Excel for Mac v. 16.75 were used for the statistical analysis.

3 | RESULTS

The total number of included patients was 102, of whom 27 had only 1 DIC and 20 had all 3 DICs. The number of analysed reports was 141, with 46 cases of leucopenia, 71 cases of anaemia and 80 cases of thrombocytopenia. The criteria for the minimum number of cases per DIC were met.

In our study, the reason for hospitalization in more than 50% of patients was either circulatory, respiratory or digestive disease, where the majority (63.0%) of patients survived and were discharged home. Most cases were female, and the average age of patients was 63.6 ± 16.3 years, with the youngest patient being 20.4 years and the oldest 91.8 years at the DIC occurrence. Regardless of DIC, each patient during the hospital stay received more than 27 different drugs (calculation based on the INN), of which 15 drugs have the potential to cause cytopenia of interest according to their summaries of product characteristics. Detailed results for each DIC are presented in Table 1.

Regardless of the type of DIC, the hospital stay was more than 25 days, with >16 specialist consultations, including at least 1 haematologist consultation. The number of biochemistry analyses was nearly 25, meaning that patients had this type of analysis almost every day. The most utilized morphological diagnostic service was X-ray imaging. Transfusion was administered in more than half of the patients with anaemia or thrombocytopenia, wherein the severity of grades ≥3, 2 out of 3 patients had transfusion received. Results on the healthcare utilization data are presented in Table 2.

Leucopenia had the highest average costs per case, followed by thrombocytopenia and anaemia. The average total cost of 1 case of DIC for leucopenia was 200 928.4 ± 125 838.4 RSD (1880.9 USD, 18.2% GDP per capita, 7.0% GDP per capita, PPP). This result indicates that the cost of treating 1 case of leucopenia is about 7% of the average person's annual income, which represents a substantial economic burden for 1 ADR. The cost per case of anaemia was 109 502.5 ± 68 604.2 RSD (1036.8 USD, 7.5% GDP per capita, 2.9% GDP per capita, PPP), while for thrombocytopenia, it was 115 065.2 ± 73 064.2 RSD (1100.6 USD, 7.4% GDP per capita, 2.8% GDP per capita, PPP). Our results show that the costs of leucopenia grade 1–2 were higher than the costs of more severe leucopenia.

About 50% of the total costs were related to drug utilization in leucopenia, which was not the case for anaemia (∼1%) or thrombocytopenia (∼5%). Transfusion costs were around 6–8% of total costs.

Results on costs expressed in absolute value (RSD) of managing DICs are presented in Table 3.

The total cost of hospitalization, visits to specialists, laboratory analysis, morphological diagnostics, transfusions, drugs and cost per case of leucopenia or anaemia or thrombocytopenia expressed as % GDP per capita and %GDP per capita PPP is presented in Figure 2.

Detailed results of costs converted to US dollars and expressed as GDP per capita and GDP per capita PPP are given in the *Appendix file*.

It can be seen from Figure 2 that the costs of drugs in the case of leucopenia had the largest share. The costs for other healthcare services were similar between leucopenia, anaemia and thrombocytopenia cases.

GLMs are linear regression models exploring potential predictors of nonchemotherapy DIC costs. Three separate GLMs were created using the γ distribution and log link function, 1 for each DIC. The model for leucopenia had a goodness of fit (value /df = 0.097), Pearson chi-square (value /df = 0.094), AIC (1145.223) and an Omnibus test (86.502, $P < .001$). The model for anaemia had a goodness of fit (value /df = 0.038), Pearson chi-square (value /df = 0.036), AIC (1611.080) and an Omnibus test (182.567, $P < .001$). The model for thrombocytopenia had a goodness of fit (value /df = 0.055), Pearson chi-square (value/df = 0.055), AIC (1850.622) and Omnibus test (178.068, $P < .001$).

TABLE 1 Characteristics of the study sample.

Variables		Leucopenia (*N* = 46)	Anaemia (*N* = 71)	Thrombocytopenia (*N* = 80)	*P*-value
Age (years)		59.8 ± 15.8 (62.9; 20.4)	63.7 ± 15.5 (66.5; 19.9)	65.7 ± 15.4 (69.1; 19.5)	.102
Sex (*n*)	*male*	27 (58.7%)	39 (54.9%)	47 (58.8%)	0.884
	female	19 (41.3%)	32 (45.1%)	33 (41.3%)	
Patient status (*n*)	*live*	29 (63.0%)	48 (67.6%)	48 (6.0%)	0.651
	dead	17 (37.0%)	23 (32.4%)	32 (4.0%)	
Average number of drugs* (*n*)		27.2 ± 11.6 (25.5; 15.5)	29.4 ± 11.4 (28.0; 15.5)	29.9 ± 10.8 (28.0; 14.3)	.403
Average number of drugs with cytopenia of interest in SPC* (*n*)		14.3 ± 5.9 (14.0; 8.0)	15.0 ± 5.4 (15.0; 7.5)	14.9 ± 5.4 (15.0; 6.3)	.768
Adverse reaction severity (*n*)	*Grade 1–2*	42 (91.3%)	35 (49.3%)	42 (52.5%)	<.001
	Grade ≥ 3	4 (8.7%)	36 (50.7%)	38 (47.5%)	

Note: Continuous variables are described by mean ± standard deviation (median; interquartile range). Categorical variables are described by rate and percentage.

Abbreviations: INN, International Nonproprietary Name; *N*, number of cases; SPC, summary of product characteristics.

*calculated on the basis of the INN number of drugs.

TABLE 2 Healthcare services utilization.

	Leucopenia ($N = 46$)	Anaemia ($N = 71$)	Thrombocytopenia ($N = 80$)
Average number of hospital days	**28.5 ± 18.4 (26.5; 19.5)**	**27.4 ± 19.1 (22.0; 17.0)**	**25.8 ± 18.4 (20.5; 19.0)**
Grade 1–2	*29.5 ± 18.8 (28.0; 20.3)*	*25.9 ± 19.8 (20.0; 17.0)*	*26.3 ± 16.6 (20.5; 19.5)*
Grade ≥ 3	*18.0 ± 9.5 (19.5; 18.0)*	*28.8 ± 18.6 (24.0; 17.3)*	*25.3 ± 20.3 (19.5; 20.5)*
Average number of specialist consultations	**17.5 ± 12.2 (15.5; 13.0)**	**16.1 ± 10.7 (14.0; 14.0)**	**17.1 ± 10.6 (15.0; 13.0)**
Grade 1–2	*18.3 ± 12.4 (16.0; 13.3)*	*14.1 ± 9.4 (11.0; 12.0)*	*16.8 ± 9.3 (15.0; 9.0)*
Grade ≥ 3	*9.5 ± 4.9 (9.0; 9.0)*	*18.1 ± 11.6 (16.0; 16.8)*	*17.4 ± 11.9 (16.5; 17.0)*
Average number of haematologist consultations	**1.5 ± 1.9 (1.0; 2.0)**	**1.3 ± 1.7 (1.0; 2.0)**	**1.6 ± 1.9 (1.0; 2.0)**
Grade 1–2	*1.6 ± 1.9 (1.0; 2.0)*	*0.8 ± 1.1 (0.0; 1.0)*	*1.0 ± 1.4 (0.0; 1.3)*
Grade ≥ 3	*1.0 ± 0.8 (1.0; 1.5)*	*1.8 ± 2.1 (1.0; 4.0)*	*2.2 ± 2.2 (1.0; 3.3)*
Average number of biochemistry analyses	**24.9 ± 15.4 (21.0; 19.3)**	**24.4 ± 18.1 (19.0; 18.0)**	**25.0 ± 17.1 (20.0; 17.5)**
Grade 1–2	*25.7 ± 15.8 (22.5; 20.0)*	*19.7 ± 12.9 (17.0; 19.0)*	*24.0 ± 15.2 (19.5; 16.0)*
Grade ≥ 3	*15.8 ± 6.8 (15.5; 12.8)*	*29.0 ± 21.1 (22.0; 30.5)*	*26.2 ± 19.2 (21.5; 20.3)*
Average number of blood count analyses	**16.3 ± 12.2 (12.5; 16.0)**	**16.2 ± 12.4 (13.0; 15.0)**	**16.5 ± 12.2 (13.0; 13.0)**
Grade 1–2	*16.7 ± 12.4 (12.5; 15.3)*	*12.8 ± 8.7 (12.0; 12.0)*	*15.0 ± 8.9 (12.5; 12.5)*
Grade ≥ 3	*12.5 ± 10.0 (12.0; 18.5)*	*19.6 ± 14.6 (16.0; 14.0)*	*18.2 ± 15.0 (13.0;14.3)*
Average number of microbiological analyses	**3.1 ± 2.9 (2.0; 4.0)**	**2.8 ± 3.2 (2.0; 4.0)**	**2.9 ± 3.2 (2.0; 3.0)**
Grade 1–2	*3.2 ± 3.0 (2.0; 4.3)*	*2.7 ± 3.7 (2.0; 3.0)*	*2.9 ± 3.0 (2.0; 5.0)*
Grade ≥ 3	*2.0 ± 0.0 (2.0; 0.0)*	*2.9 ± 2.8 (2.0; 3.0)*	*2.8 ± 3.4 (2.0; 2.0)*
Average number of CT scans	**1.2 ± 1.1 (1.0; 2.0)**	**1.3 ± 1.2 (1.0; 2.0)**	**1.3 ± 1.2 (1.0; 2.0)**
Grade 1–2	*1.2 ± 1.1 (1.0; 2.0)*	*1.1 ± 1.3 (1.0; 1.0)*	*1.2 ± 1.2 (1.0; 2.0)*
Grade ≥ 3	*0.8 ± 1.0 (0.5; 1.8)*	*1.4 ± 1.1 (1.0; 1.0)*	*1.3 ± 1.3 (1.0; 1.3)*
Average number of X-ray images	**4.7 ± 4.6 (3.5; 3.3)**	**4.7 ± 5.5 (3.0; 4.0)**	**4.6 ± 5.0 (3.0; 3.8)**
Grade 1–2	*4.9 ± 4.8 (3.5; 4.0)*	*4.3 ± 3.6 (4.0; 3.0)*	*4.4 ± 2.8 (4.0; 4.0)*
Grade ≥ 3	*2.8 ± 2.2 (3.0; 4.3)*	*5.2 ± 6.9 (3.0; 5.8)*	*4.8 ± 6.6 (3.0; 3.5)*
Average number of MRIs	**0.1 ± 0.5 (0.0; 0.0)**	**0.1 ± 0.4 (0.0; 0.0)**	**0.1 ± 0.4 (0.0; 0.0)**
Grade 1–2	*0.1 ± 0.5 (0.0; 0.0)*	*0.1 ± 0.2 (0.0; 0.0)*	*0.1 ± 0.2 (0.0; 0.0)*
Grade ≥ 3	*0.0 ± 0.0 (0.0; 0.0)*	*0.2 ± 0.5 (0.0; 0.0)*	*0.2 ± 0.5 (0.0; 0.0)*
Average number of ECGs	**1.0 ± 0.9 (1.0; 2.0)**	**1.2 ± 2.0 (1.0; 1.0)**	**1.1 ± 1.3 (1.0; 2.0)**
Grade 1–2	*1.0 ± 0.9 (1.0; 2.0)*	*1.5 ± 2.7 (1.0; 1.0)*	*1.2 ± 1.4 (1.0; 2.0)*
Grade ≥ 3	*1.00 ± 0.8 (1.0; 2.0)*	*0.8 ± 0.9 (1.0; 1.8)*	*1.1 ± 1.2 (1.0; 2.0)*
TRANSFUSION *n* (%)	Not applicable	**43 (60.6%)**	**45 (56.3%)**
Grade 1–2		*14 (32.6%)*	*13 (28.9%)*
Grade ≥ 3		*29 (67.4%)*	*32 (71.1%)*

Note: Variables are described by mean ± standard deviation (median; interquartile range).
Abbreviations: CT, computed tomography; ECG, electrocardiogram; MRI, magnetic resonance imaging; *N*, number of cases.

Table 4 shows the results of the multivariate analysis, with only significant factors associated with the total costs of DICs. In leucopenia cases, patients who died (coefficient of the GLM [B] = 0.293, $P = .020$) and were older (B = 0.010, $P = .004$) had significantly higher costs. Factors showing a decrease in total costs were seen only in anaemia, such as the administration of transfusion (B = − 0.152, $P = .004$) and a higher number of X-ray images (B = − 0.013, $P = .042$). The duration of hospitalization was significant, considering the total costs for patients with anaemia and thrombocytopenia. The number of CTs was the only factor shown to impact total costs for all DICs. Factors found to have a significant influence on total costs are shown in Table 4.

4 | DISCUSSION

Leucopenia has been shown to have the highest costs among nonchemotherapy DICs, primarily because it requires the use of numerous more expensive drugs (primarily antibiotics). In the case of anaemia and thrombocytopenia, most of the costs were from hospitalization (number of hospital days), while drug costs were significantly lower if the use of transfusions was excluded. The costs of laboratory diagnostics for all 3 types of disorders were higher than the morphological diagnostics costs. The total costs of consulting a doctor were the lowest, except for anaemia, where the costs

TABLE 3 The total cost of healthcare services, transfusion, drugs and cost per case of leucopenia, anaemia or thrombocytopenia in Serbian dinars.

COST TYPE	Leucopenia ($N = 46$)	Anaemia ($N = 71$)	Thrombocytopenia ($N = 80$)
COST OF HOSPITALIZATION	**43 976.7 ± 28 465.4 (40 953.1; 30 135.3)**	**42 270.0 ± 29 490.3 (33 998.8; 26 271.8)**	**39 907.0 ± 28 382.9 (31 680.7; 29 362.6)**
Grade 1–2	*45 515.7 ± 29 080.9 (43 271.2; 31 294.4)*	*40 047.9 ± 30 515.5 (30 908.0; 26 271.8)*	*40 658.7 ± 25 686.6 (31 680.7; 30 135.3)*
Grade ≥ 3	*27 817.2 ± 14 661.0 (30 135.3; 27 817.2)*	*44 430.3 ± 28 723.3 (37 089.6; 26 658.2)*	*39 082.4 ± 31 425.6 (30 135.3; 31 680.7)*
COSTS OF VISISTS TO SPECIALIST	**4595.1 ± 3102.3 (4079.9; 3312.7)**	**4236.1 ± 2731.2 (3697.7; 3567.5)**	**4481.3 ± 2690.0 (3952.5; 3312.7)**
Grade 1–2	*4789.8 ± 3162.4 (4207.3; 3376.4)*	*3712.3 ± 2398.4 (2933.2; 3057.9)*	*4413.6 ± 2362.0 (3952.5; 2293.4)*
Grade ≥ 3	*2551.0 ± 1257.0 (2423.6; 2293.4)*	*4745.3 ± 2964.7 (4207.3; 4268.3)*	*4556.1 ± 3042.6 (4334.8; 4332.0)*
Costs of specialist consultations excl. Haematologist	**4082.7 ± 2878.2 (3694.9; 3376.4)**	**3779.3 ± 2572.1 (3312.7; 3057.9)**	**3949.8 ± 2499.1 (3567.5; 2803.1)**
Grade 1–2	*4265.3 ± 2925.6 (3822.4; 3376.4)*	*3385.5 ± 2336.8 (2803.1; 3057.9)*	*4034.7 ± 2249.8 (3567.5; 2357.1)*
Grade ≥ 3	*2166.0 ± 1388.0 (1911.2; 2548.2)*	*4162.1 ± 2760.7 (3440.1; 3758.6)*	*3855.9 ± 2776.4 (3312.7; 4140.9)*
Costs of haematologist consultations	**512.4 ± 473.7 (385.0; 509.7)**	**456.8 ± 443.9 (385.0; 509.7)**	**531.5 ± 492.9 (385.0; 509.7)**
Grade 1–2	*524.5 ± 491.3 (385.0; 509.7)*	*326.8 ± 283.8 (130.2; 254.8)*	*378.9 ± 366.9 (130.2; 318.5)*
Grade ≥ 3	*385.0 ± 208.1 (385.0; 382.2)*	*583.2 ± 531.4 (385.0; 1019.3)*	*700.2 ± 560.3 (385.0; 828.2)*
COSTS OF LABORATORY ANALYSIS	**33 375.0 ± 20 215.0 (29 514.1; 29 430.5)**	**32 533.5 ± 23 149.0 (26 914.8; 27 631.4)**	**33 219.5 ± 22 014.9 (27 725.0; 27 069.9)**
Grade 1–2	*34 457.8 ± 20 684.6 (30 398.2; 32 116.0)*	*26 885.8 ± 18 085.8 (23 750.1; 23 994.0)*	*31 845.0 ± 19 313.2 (27 960.2; 23 402.3)*
Grade ≥ 3	*22 005.4 ± 96 72.8 (21 240.7; 17 784.4)*	*38 024.3 ± 26 288.7 (28 897.2; 33 493.7)*	*34 738.7 ± 24 838.8 (27 725.0; 28 568.5)*
Costs of biochemistry	**22 396.3 ± 13 897.4 (18 928.1; 17 350.8)**	**22 025.7 ± 16 266.8 (17 125.5; 16 224.1)**	**22 533.5 ± 15 426.8 (18 026.8; 15 773.5)**
Grade 1–2	*23 177.3 ± 14 214.3 (20 280.2; 18 026.8)*	*17 795.0 ± 11 634.2 (15 322.8; 17 125.5)*	*21 589.2 ± 13 662.2 (17 576.1; 14 421.4)*
Grade ≥ 3	*14 196.1 ± 6129.8 (13 970.8; 11 492.1)*	*26 138.9 ± 19 037.6 (19 829.5; 27 490.9)*	*23 577.2 ± 17 296.5 (19 378.8; 18 252.1)*
Costs of blood count	**5862.4 ± 4373.5 (4494.5; 5753.0)**	**5839.1 ± 4467.2 (4674.3; 5393.4)**	**5941.7 ± 4381.3 (4674.3; 4674.3)**
Grade 1–2	*5992.7 ± 4455.4 (4494.5; 5483.3)*	*4592.1 ± 3110.3 (4314.7; 4314.7)*	*5402.0 ± 3183.0 (4494.5; 4494.5)*
Grade ≥ 3	*4494.5 ± 3589.6 (4314.7; 6651.9)*	*7051.4 ± 5239.0 (5753.0; 5033.8)*	*6538.3 ± 5391.0 (4674.3; 5123.7)*
Costs of microbiological analysis	**5116.3 ± 4788.6 (3314.8; 6629.6)**	**4668.7 ± 5376.5 (3314.8; 6629.6)**	**4744.3 ± 5252.7 (3314.8; 4972.2)**
Grade 1–2	*5287.9 ± 4982.1 (3314.8; 7043.9)*	*4498.6 ± 6143.4 (3314.8; 4972.2)*	*4853.8 ± 4943.7 (3314.8; 8287.0)*
Grade ≥ 3	*3314.8 ± 0.0 (3314.8; 0.0)*	*4834.1 ± 4592.7 (3314.8; 4972.2)*	*4623.3 ± 5639.1 (3314.8; 3314.8)*
COSTS OF MORHOLOGICAL DIAGNOSTIC SERVICES	**20 648.4 ± 16 804.3 (17 766.5; 27 382.9)**	**22 023.8 ± 18 958.2 (17 066.5; 25 732.9)**	**21 852.6 ± 18 566.1 (16 666.5; 25 132.9)**
Grade 1–2	*21 398.2 ± 17 014.1 (17 766.5; 26 482.9)*	*19 430.6 ± 18 653.0 (16 466.5; 22 166.5)*	*20 656.4 ± 16 982.7 (16 116.5; 28 482.9)*
Grade ≥ 3	*12 774.9 ± 13 748.2 (10 283.2; 25 741.3)*	*24 544.9 ± 19 172.2 (20 911.2; 18 919.5)*	*23 174.7 ± 20 321.7 (17 316.5; 17 583.1)*
Costs of CT	**16 043.3 ± 15 055.0 (13 666.5; 27 332.9)**	**17 323.7 ± 16 327.7 (13 666.5; 27 332.9)**	**17 253.9 ± 16 523.8 (13 666.5; 27 332.9)**
Grade 1–2	*16 595.0 ± 15 252.9 (13 666.5; 27 332.9)*	*15 228.4 ± 17 467.5 (13 666.5; 13 666.5)*	*16 595.0 ± 15 839.0 (13 666.5; 27 332.9)*
Grade ≥ 3	*10 249.9 ± 13 084.7 (6833.2; 23 916.3)*	*19 360.8 ± 15 103.9 (13 666.5; 13 666.5)*	*17 982.2 ± 17 433.8 (13 666.5; 17 083.1)*

(Continues)

TABLE 3 (Continued)

COST TYPE	Leucopenia ($N = 46$)	Anaemia ($N = 71$)	Thrombocytopenia ($N = 80$)
Costs of RTG	**3302.2 ± 3248.8 (2450.0; 2275.0)**	**3302.8 ± 3836.2 (2100.0; 2800.0)**	**3237.5 ± 3478.5 (2100.0; 2625.0)**
Grade 1–2	*3433.3 ± 3347.5 (2450.0; 2800.0)*	*2980.0 ± 2497.2 (2800.0; 2100.0)*	*3100.0 ± 1974.7 (2800.0; 2800.0)*
Grade ≥ 3	*1925.0 ± 1552.2 (2100.0; 2975.0)*	*3616.7 ± 4813.5 (2100.0; 4025.0)*	*3389.5 ± 4633.4 (2100.0; 2450.0)*
Costs of MRI	**716.0 ± 2484.4 (0.0; 0.0)**	**695.8 ± 2259.4 (0.0; 0.0)**	**686.2 ± 2205.3 (0.0; 0.0)**
Grade 1–2	*784.2 ± 2592.2 (0.0; 0.0)*	*313.7 ± 1292.8 (0.0; 0.0)*	*261.4 ± 1183.2 (0.0; 0.0)*
Grade ≥ 3	*0.0 ± 0.0 (0.0; 0.0)*	*1067.4 ± 2880.7 (0.0; 0.0)*	*1155.7 ± 2898.5 (0.0; 0.0)*
Costs of ECG	**587.0 ± 558.4 (600.0; 1200.0)**	**701.4 ± 1199.9 (600.0; 600.0)**	**675.0 ± 760.0 (600.0; 1200.0)**
Grade 1–2	*585.7 ± 569.8 (600.0; 1200.0)*	*908.6 ± 1596.6 (600.0; 600.0)*	*700.0 ± 826.7 (600.0; 1200.0)*
Grade ≥ 3	*600.0 ± 489.9 (600.0; 900.0)*	*500.0 ± 564.7 (600.0; 1050.0)*	*647.4 ± 688.8 (600.0; 1200.0)*
COSTS OF TRANSFUSION	**Not applicable**	**7324.2 ± 16 796.8 (3000.0; 8500.0)**	**10 023.8 ± 22 377.8 (1600.0; 11200.0)**
Grade 1–2		*4835.0 ± 11051.0 (0.0; 4400.0)*	*1976.2 ± 4132.6 (0.0; 1575.0)*
Grade ≥ 3		*9744.4 ± 20 818.5 (6400.0; 6975.0)*	*18 918.4 ± 29 925.0 (8250.0; 20 475.0)*
COSTS OF DRUGS	**98 333.2 ± 91 848.2 (88 894.6; 69 214.6)**	**1115.1 ± 742.1 (843.2; 116.7)**	**5578.2 ± 26847.0 (843.2; 4222.1)**
Grade 1–2	*98 006.7 ± 93 123.4 (88 894.6; 69 214.6)*	*1103.8 ± 763.3 (843.2; 108.8)*	*2351.1 ± 2047.6 (843.2; 4222.1)*
Grade ≥ 3	*101 760.8 ± 89 483.1 (78 125.6; 164 386.2)*	*1126.0 ± 731.7 (959.9; 116.7)*	*9144.9 ± 38850.8 (843.2; 4222.1)*
TOTAL COST PER CASE	**200 928.4 ± 125 838.4 (176 078.4; 171 223.4)**	**109 502.5 ± 68 604.2 (90 267.3; 74 225.1)**	**115 065.2 ± 73 064.2 (89 732.4; 77 755.9)**
Grade 1–2	*204 168.3 ± 127 281.5 (176 078.4; 168 943.4)*	*96 015.4 ± 57 262.1 (87 785.6; 47 784.1)*	*101 901.0 ± 53 480.4 (88 017.0; 60 569.3)*
Grade ≥ 3	*166 909.2 ± 120 131.4 (149 262.8; 228 768.1)*	*122 615.1 ± 76 609.7 (97 858.0; 92 546.6)*	*129 615.1 ± 88 400.6 (93 665.5; 102 073.9)*

Note: Variables are described by mean ± standard deviation (median; interquartile range).
Abbreviations: CT, computed tomography; ECG, electrocardiogram; MRI, magnetic resonance imaging; *N*, number of cases.

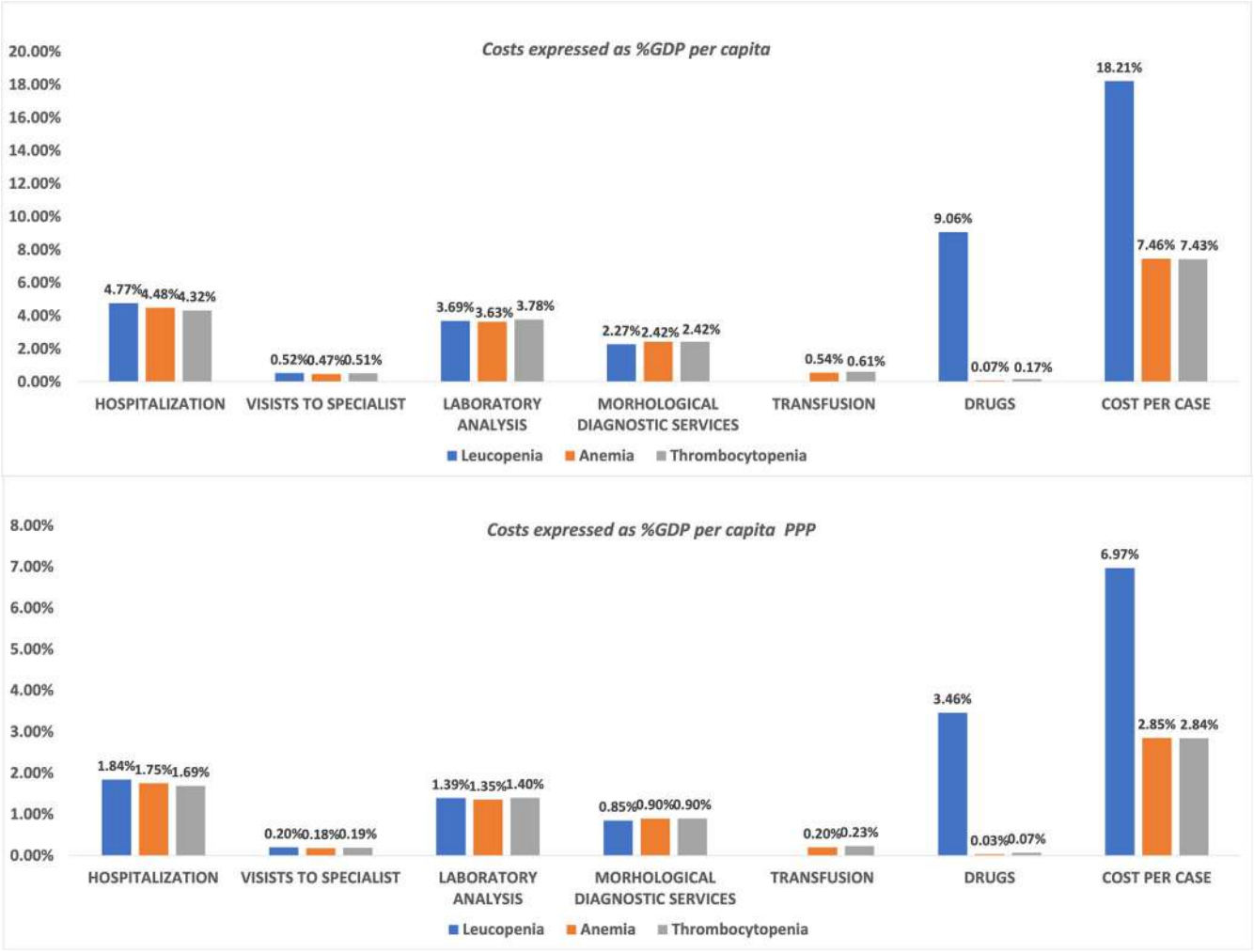

FIGURE 2 Total cost of hospitalization, visits to specialist, laboratory analysis, morphological diagnostic, transfusion, drugs and cost per case of leucopenia, anaemia or thrombocytopenia expressed as %GDP per capita and %GDP per capita PPP. GDP, gross domestic product; PPP, purchasing power parity.

of drugs were even lower. The factors that had the greatest influence on the total costs of anaemia and thrombocytopenia of nonchemotherapy DICs were the length of hospitalization, the number of CTs and the number of laboratory tests. The overall cost of leucopenia treatment was most influenced by survival status, age and the number of laboratory tests.

In the case of leucopenia, it is interesting that the average treatment costs per case were lower with the increase in severity of leucopenia due to shorter hospitalization, but this may not reflect the actual situation because the number of cases in our study with grade ≥3 was very small ($n = 4$, 8.7%). The costs of treating leucopenia mainly depend on the cause of the infection as a complication of leucopenia and the severity of the infection. More severe infections that turn into sepsis require the use of reserve antibiotics or prolonged treatment, which therefore increases the total costs, which is in line with the results of our study (3/4 of the total costs are due to drugs and hospitalization).[36,37] This suggests that future research should be stratified not only by severity grade but also by the presence of infection or sepsis, as these factors, rather than grade alone, may be the cost drivers.

The treatment of anaemia and thrombocytopenia in already hospitalized patients, as a consequence of using nonchemotherapy drugs, is primarily based on the transfusion of erythrocytes or platelets because urgent correction of the number of these blood cells is often necessary. Transfusion itself leads to prolonged hospitalization[38,39] and a state of partial immunosuppression,[40] which creates the conditions for the occurrence of additional hospital infections, additional prolongation of hospitalization and increased costs. Hence, with these disorders, the length of hospitalization is a significant factor that increases the total costs. The length of hospitalization is recognized in many COI studies as 1 of the main cost generators.[17,21,41]

The costs per case in our study ranged from around 900 to 1900 USD, depending on the type and grade of cytopenia. This aligns with some COI studies on specific cytopenia or ADR.[16,42] Meanwhile, 1 study in France estimated the cost of 1 case of heparin-induced thrombocytopenia at 3500 EUR (~4300 USD).[22]

TABLE 4 Factors associated with the costs of treating nonchemotherapy drug-induced cytopenias.

VARIABLE	B (95%CI)	*P*
Drug-induced leucopenia		
Died *(0, no; 1, yes)*	0.293 (0.046 to 0.54)	.020
Age	0.010 (0.003 to 0.016)	.004
Number of blood count	0.014 (0.001 to 0.027)	.035
Number of microbiological analyses	0.048 (0.016 to 0.079)	.003
Number of computed tomography scans	0.092 (0.007 to 0.176)	.034
Drug-induced anaemia		
Transfusion *(0, no; 1, yes)*	−0.152 (−0.256 to −0.049)	.004
Number of hospital days	0.014 (0.010 to 0.018)	.000
Number of biochemical analyses	0.009 (0.002 to 0.016)	.018
Number of computed tomography scans	0.114 (0.067 to 0.162)	.000
Number of X-ray images	−0.013 (−0.026 to 0.000)	.042
Drug-induced thrombocytopenia		
Sex *(0, male; 1, female)*	0.111 (0.011 to 0.211)	.029
Number of hospital days	0.010 (0.005 to 0.014)	.000
Number of biochemical analyses	0.010 (0.002 to 0.018)	.020
Number of microbiological analyses	0.024 (0.002 to 0.046)	.031
Number of computed tomography scans	0.107 (0.060 to 0.154)	.000
Number of electrocardiograms	0.067 (0.022 to 0.112)	.004

Abbreviations: B, coefficient of the generalized linear model; CI confidence interval.

Regardless of the number of consultations by a specialist, the total costs of consultations are very low due to the low unit price in the Republic of Serbia, which is administratively regulated by the HIF[29] and differs from the market-based prices at real costs. For example, the price of a specialist consultation in the private sector is >20–30 times higher because they are formed based on the realistic supply and demand principle.[29,43,44]

Although several factors have been found to be associated with the total costs per case of each DIC, the effect of many of them is indirect through the prolongation of hospitalization (e.g., older patients are hospitalized longer),[45,46] and survival is also related to the length of hospitalization.[47] Longer hospitalization also means a greater number of laboratory analyses as well as more frequent morphological diagnostics (CT, X-ray, electrocardiogram etc.). Even in our study, where the administratively regulated cost of a hospital day is very low (<15 EUR), hospitalization is the main driver of total costs. In countries where hospitalization prices are market-based, in higher-income countries, total costs are significantly higher.[48]

4.1 | Limitations of the study

The main limitation of our study is that it is a single-centre study, and the results reflect the influence of local practice, which could be different in other countries. Being the first global study on this topic, its current external validity is low. This limitation may be overcome through future research conducted in accordance with our study plan and methodology, or by applying a similar microcosting methodology on this topic.

Our study considered the number of cases rather than the number of patients since cytopenias are often not limited to a single disorder (e.g., anaemia associated with thrombocytopenia).

Because these events are rare and many ADRs go unreported, our data probably represent the more severe end of the spectrum (only in hospitalized patients due to other disorder). Thus, while the costs per case are high, the overall incidence is low.

Although our study was sufficiently powered to obtain results relevant to the population, some important factors influencing costs could have gone unnoticed because the extent of their influence may have required a higher sample size.

Additional limitations are that we only included direct costs and the excessive length of data collection (>1 year), which are also seen in other studies with the same design (bottom-up, microcosting).[17,24,46]

4.2 | Strengths of the study

There were no studies focused on nonchemotherapy DICs; rather, they focused on a single drug (e.g., heparin, ribavirin), while our study focused on drug-induced blood disorders often seen in practice.[21–23] We used a bottom-up microcosting approach, which represents the gold standard when conducting COI studies. Data collected in our studies are real-world data at the level of a single patient where healthcare services, drugs or transfusion utilization was extracted on a unit level (e.g., disorder grade was determined by analysing every blood analysis, number of INN determined having each daily therapy of patient assessed). Also, in our study, causality was assessed by an expert in clinical pharmacology.

Considering that this is 1 of the first studies focusing on the costs of nonchemotherapy DICs, we expressed our results also in %GDP per capita and %GDP per capita PPP so the other countries could easily estimate these costs in their countries. Also, in case the other countries have significant differences in healthcare service prices compared to Serbia, we provided a healthcare services utilization so costs could be calculated by multiplying them with unit costs.

The methodology of our study may serve as a basis for future multicentre studies across Europe and globally, as there is currently no harmonized microcosting methodology in place. This would ensure consistent data collection, the same inclusion and exclusion criteria, cost calculations and analysis, and results that could be comparable between countries.

Nonchemotherapy DICs are relatively rare in clinical practice and often unrecognized, leading to an underestimation of the resulting costs. Clinicians should not overlook these cytopenias, and perhaps they should implement monitoring or preventive strategies for high-risk medications to potentially avoid these costly outcomes. Pharmacoeconomic evaluations of drugs (especially those known to cause cytopenias in rare cases) should include the possibility of these ADR costs in their models.

This study showed that the use of healthcare services and costs caused by nonchemotherapy drugs are considerable. Our findings underscore the importance of considering even infrequent adverse reactions in the overall cost profile of drug therapies. Implementation of proactive strategies to manage and prevent DICs could not only improve patient outcomes but also reduce healthcare costs.

AUTHOR CONTRIBUTIONS

Ivana Stević: Conceptualization; methodology; software; formal analysis; data curation; writing–original draft preparation; visualization; investigation; validation; writing–reviewing and editing. **Slobodan M. Janković:** Conceptualization; methodology; software; formal analysis; data curation; writing–original draft preparation; visualization; investigation; supervision; validation; writing–reviewing and editing. **Nataša Čanak-Baltić:** Data curation; writing–original draft preparation; writing–reviewing and editing. **Nemanja Petrović:** Data curation; writing–original draft preparation; writing–reviewing and editing. **Valentina Marinković:** Data curation; writing–original draft preparation; writing–reviewing and editing; funding acquisition. **Dragana Lakić:** Conceptualization; methodology; software; formal analysis; data curation; writing–original draft preparation; visualization; investigation; supervision; validation; writing–reviewing and editing.

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CONFLICT OF INTEREST STATEMENT

Authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data on which this manuscript is based are available to all interested parties on reasonable request from the corresponding author.

ETHICS APPROVAL STATEMENT

The research was approved by the Ethics Committee of Clinical Center of Kragujevac (decision number: 01/22–340 from 10 October 2022). The need for informed consent was waived by the Ethics Committee due to the retrospective nature of the research.

ORCID

Ivana Stević https://orcid.org/0000-0001-8880-7092

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SUPPORTING INFORMATION

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Cytopenias as Adverse Drug Reactions: A 10-Year Analysis of Reporting Structure, Rate, and Trend

Ivana Stević [1,*], Slobodan M. Janković [2], Marija Mihailović [3], Ivana Jović [3], Marina Odalović [1], Valentina Marinković [1] and Dragana Lakić [1]

[1] Department of Social Pharmacy and Pharmaceutical Legislation, Faculty of Pharmacy, University of Belgrade, 11221 Belgrade, Serbia
[2] Department of Pharmacology and Toxicology, Faculty of Medical Sciences, University of Kragujevac, 34000 Kragujevac, Serbia
[3] National Pharmacovigilance Centre, Medicines and Medical Devices Agency of Serbia, 11221 Belgrade, Serbia
* Correspondence: ivana.stevic@pharmacy.bg.ac.rs

Abstract

Background/Objectives: Underreporting is very common in drug-induced cytopenias (DICs) due to the late onset of symptoms and the need for laboratory confirmation and monitoring. This research aimed to analyze spontaneously reported adverse drug reaction (ADR) cases of leucopenia, anemia, thrombocytopenia, and total cytopenia, including their reporting structure, rate, and trend, globally (World) and in Serbia. **Methods**: Based on real-world data from VigiBase, analyses of the DIC reporting structure, rate, and trend over 10 years (2014–2023) were performed. The reporting rate was calculated and expressed as the number of reports per 1,000,000 inhabitants per year (ADR/million/year). Statistics included descriptions, a chi-square test, joinpoint analysis, and measures of variability. **Results**: Leucopenia was reported more often in Serbia compared to World (1.26 versus 0.96 reports/million/year, respectively), anemia more often in World (2.09 versus 1.75 reports/million/year), while thrombocytopenia reporting was comparable (1.83 reports/million/year globally versus 1.82 reports/million/year in Serbia). In Serbia, there was a constant increase in reporting throughout the observed period, regardless of the cytopenia type, while globally, anemia reports decreased over time. Most of the reported DICs were serious and occurred in females aged 45–64 years. In Serbia, 76.34% of DICs were reported by physicians compared to 31.72% globally. **Conclusions**: Although upward trends in DIC reporting are observed, variability in reporting between years was greater in Serbia than in World. Many measures are needed to promote the early detection of DICs, with the priority of increasing access to blood count results for all healthcare workers, including pharmacists.

Keywords: adverse drug reaction; anemia; leucopenia; thrombocytopenia; pharmacovigilance

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1. Introduction

Cytopenias represent "a condition in which the number of blood cells is lower than normal", i.e., a decrease in the number of erythrocytes, lower hemoglobin concentration levels (below 130 g/L in men and 120 g/L in women (anemia)), leukocyte counts below 4.5×10^9/L (leucopenia), or platelet counts below 150×10^9/L (thrombocytopenia). If all three disorders are present simultaneously, the disorder is called pancytopenia [1–4].

Factors driving cytopenias are numerous and can be hereditary or acquired [4,5]. In acquired cytopenias, there are various underlying mechanisms (e.g., effects on bone marrow,

autoimmune disorders, nutritional deficiencies, viruses, alcohol, ionizing radiation, etc.), including drugs (drug-induced cytopenia—DIC) [5–7]. In addition to anticancer drugs, DIC may be induced by antibiotics, nonsteroidal anti-inflammatory drugs, antihypertensives, antiarrhythmics, antiepileptics, and many others [5,7,8].

The incidence of thrombocytopenia is estimated at 10/1,000,000 people per year [7], and neutropenia caused by non-anticancer drugs is estimated at 2.4–15.4 cases per million people per year, with a mortality rate of 5% [9]. Anemia caused by any drug type varies from 1 to 4 cases per million people per year [10], and its mortality rate can be from 4% to 70% [7,11].

The costs resulting from adverse drug reactions (ADRs) are estimated at 30–137 billion dollars per year in the United States [12,13]. In the literature, the cost per ADR varies between USD 65.0 and USD 12,129.90 [14], with the cost per ADR in high-income countries being 10 times higher than that in low- or middle-income countries [14]. One study estimated the cost per case of treating heparin-induced thrombocytopenia in France to be around EUR 3500 [15], while another in Germany estimated that of treating agranulocytosis and anemia at EUR 1240 and 880, respectively [16].

The satisfactory safety (benefits outweigh the risks under prescribed use) of an authorized drug is guaranteed by obtaining a marketing authorisation (MA) from the competent authorities. The safety data collected in clinical trials are an integral part of the documentation submitted to the authorities, and they are used to decide whether the drug meets the requirements related to the drug's safety. However, safety data from clinical trials have some limitations such as controlled conditions, the number of patients in clinical trials being significantly smaller than the actual number of patients, or some ADRs are not reported due to very low incidence. After obtaining an MA, MA holders are obliged to monitor and report data related to the drug's safety to the competent institutions and to assess the safety profile of the drug continuously [17–19].

Even with the existence of these obligations, it is estimated that reported ADRs only account for 6–10% of all ADR cases [20–22]. This is especially expressed in ADRs such as cytopenias because symptoms do not develop in the early stages and require laboratory confirmation and follow-up evaluation.

The pharmacovigilance system is defined as "a system used by an organisation to fulfil its legal tasks and responsibilities in relation to pharmacovigilance and designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance". An active surveillance system refers to a continuous, planned, and structured process for collecting safety information, whereas passive surveillance depends on healthcare professionals or patients to spontaneously report ADRs [23–25].

There are sparse references related to the structure of reported cases, rates, or trends, globally or locally, on DICs. Trend analysis of spontaneous ADR reports is an important source of information that may be a basis for planning corrective measures within the pharmacovigilance systems. However, since the trends depend heavily on pharmacotherapeutic drug groups, it is essential to determine specific trends for cytopenias as ADRs of all drugs, including non-cytostatic drugs, which are currently missing in the medical literature [26]. The aim of this research is to analyze spontaneously reported ADR cases of leucopenia, anemia, thrombocytopenia, and total cytopenia, including their structure, reporting rate (RR), and reporting trend, globally (hereafter referred also as "World") and in Serbia.

2. Results

The total number of globally reported cases of drug-induced leucopenia was 74,873, compared to 88 in Serbia. The number of reported ADR cases resulting in anemia in World was 161,631, while in Serbia, it was 122. Thrombocytopenia as an ADR was reported

globally in 141,836 cases, while in Serbia, it was reported in 126 cases. Globally, during the observed period, leucopenia was most commonly reported with cisplatin, cyclophosphamide, fluorouracil, doxorubicin, and carboplatin, in comparison to Serbia, where it was associated with methotrexate, prednisone, methylprednisolone, hydroxychloroquine, and tocilizumab. For anemia, it was most commonly reported worldwide with acetylsalicylic acid, furosemide, dexamethasone, pantoprazole, atorvastatin, and levothyroxine, while in Serbia, it was associated with methotrexate, bisoprolol, cisplatin, furosemide, metformin, pantoprazole, etc. Carboplatin, cisplatin, dexamethasone, gemcitabine, and oxaliplatin were the most common drugs suspected to cause thrombocytopenia in World, while cyclophosphamide, furosemide, methotrexate, paracetamol, prednisone, and rituximab were suspected to cause it in Serbia.

2.1. Adverse Reaction Reporting Structure

2.1.1. Leucopenia

The highest number of reported leucopenia cases was in the 45–64-year-old age group (34.19% World vs. 32.95% Serbia), and ~60% of reported cases occurred in females. In World, serious cases were reported in 45.59%, while three out of four reported cases of leucopenia in Serbia were serious. In Serbia, more than two-thirds of cases were reported by physicians (73.33%), while globally, the reporter's qualification is unknown for half of the reports.

There was a statistically significant difference in reporting across all structure categories between Serbia and World, except for the seriousness criterion. The structure of reported leucopenia cases, as well as the differences between the World and Serbia, is provided in Table 1 and the Supplementary File.

Table 1. Total reporting structure for leucopenia, anemia, thrombocytopenia, and cytopenia in total (2014–2023) in World and Serbia.

Reporting Structure Category	World N (%)	Serbia N (%)	World N (%)	Serbia N (%)	World N (%)	Serbia N (%)	World N (%)	Serbia N (%)
ADR TYPE	**Leucopenia**		**Anemia**		**Thrombocytopenia**		**Total Cytopenia**	
Number of reported ADR	N = 74,873	N = 88	N = 161,631	N = 122	N = 141,836	N = 126	N = 378,340	N = 336
PATIENT AGE	χ^2 = 22.606 *; **p = 0.003; w = 0.02**		χ^2 = 29.975 *; **p < 0.001; w = 0.01**		χ^2 = 27.381 *; **p < 0.001; w = 0.01**		χ^2 = 63.295 *; **p < 0.001; w = 0.01**	
Children (<18 years)	2612 (3.48)	3 (3.41)	4534 (2.81)	2 (1.64)	6285 (4.43)	2 (1.59)	13,431 (3.54)	7 (2.08)
Adults (18–64 years)	37,456 (50.03)	56 (63.63)	62,840 (38.87)	74 (60.66)	61,205 (43.15)	71 (56.35)	161,501 (42.69)	201 (59.82)
Elderly (≥65 years)	19,630 (26.22)	10 (11.37)	60,731 (37.58)	33 (27.05)	53,846 (37.95)	29 (23.02)	134,189 (35.47)	72 (21.43)
Unknown	15,175 (20.27)	19 (21.59)	33,526 (20.74)	13 (10.66)	20,518 (14.47)	24 (19.05)	69,219 (18.30)	56 (16.67)
SEX	χ^2 = 7.218; **p = 0.027; w = 0.01**		χ^2 = 8.606 **; **p = 0.013; w = 0.01**		χ^2 = 10.552 **; **p = 0.005; w = 0.01**		χ^2 = 15.664; **p = 0.00; w = 0.01**	
Female	43,139 (57.62)	57 (64.77)	88,291 (54.63)	81 (66.39)	62,828 (44.29)	69 (54.76)	194,258 (51.34)	207 (61.61)
Male	29,388 (39.25)	25 (28.41)	64,103 (39.66)	39 (31.97)	70,816 (49.92)	56 (44.44)	164,307 (43.43)	120 (35.71)
Unknown	2346 (3.13)	6 (6.82)	9237 (5.71)	2 (1.64)	8201 (5.78)	1 (0.79)	19,784 (5.23)	9 (2.68)
SERIOUS	χ^2 = 40.729 **; **p < 0.001; w = 0.02**		χ^2 = 2.175 **; p = 0.292; **w = 0.00**		χ^2 = 6.521 *; **p = 0.034; w = 0.00**		χ^2 = 27.376 *; **p = 0.000; w = 0.01**	
Yes	34,138 (45.59)	69 (78.41)	110,393 (68.30)	91 (74.59)	111,698 (78.75)	111 (88.10)	256,229 (67.72)	271 (80.65)
No	40,095 (53.55)	18 (20.45)	49,651 (30.72)	30 (24.59)	28,608 (20.17)	15 (11.90)	118,354 (31.28)	63 (18.75)

Table 1. *Cont.*

Reporting Structure Category	World N (%)	Serbia N (%)	World N (%)	Serbia N (%)	World N (%)	Serbia N (%)	World N (%)	Serbia N (%)
ADR TYPE	**Leucopenia**		**Anemia**		**Thrombocytopenia**		**Total Cytopenia**	
Unknown	640 (0.85)	1 (1.14)	1587 (0.98)	1 (0.82)	1530 (1.08)	0 (0.00)	3757 (0.99)	2 (0.60)
SERIOUSNESS CRITERIA	χ^2 = 2.267 *; p = 0.748; **w = 0.01**		χ^2 = 11.844 **; **p = 0.034; w = 0.01**		χ^2 = 15.371 *; **p = 0.008; w = 0.01**		χ^2 = 29.129 **; **p = 0.000; w = 0.01**	
Death	1563 (3.99)	4 (4.71)	8941 (6.31)	7 (5.43)	7377 (7.22)	9 (6.57)	17,881 (6.31)	20 (5.70)
Life threatening	2310 (5.89)	5 (5.88)	7701 (5.43)	4 (3.10)	7853 (7.68)	6 (4.38)	17,864 (6.31)	15 (4.27)
Caused/prolonged hospitalization	11,312 (28.84)	21 (24.71)	63,680 (44.92)	46 (35.66)	35,395 (34.64)	31 (22.63)	110,387 (38.98)	98 (27.92)
Disabling/incapacitating	279 (0.71)	1 (1.18)	2440 (1.72)	2 (1.55)	1229 (1.20)	1 (0.73)	3948 (1.39)	4 (1.14)
Congenital anomaly/birth defect	59 (0.15)	0 (0.00)	172 (0.12)	1 (0.78)	109 (0.11)	0 (0.00)	340 (0.12)	1 (0.28)
Other medically important condition	23,696 (60.42)	54 (63.53)	58,825 (41.50)	69 (53.49)	50,230 (49.15)	90 (65.69)	132,751 (46.88)	213 (60.68)
REPORTER QUALIFICATION	χ^2 = 190.042 *; **p < 0.001; w = 0.03**		χ^2 = 85.014 *; **p < 0.001; w = 0.02**		χ^2 = 122.737 *; **p < 0.001; w = 0.02**		χ^2 = 370.128 **; **p < 0.001; w = 0.03**	
Physician	28,375 (15.94)	66 (73.33)	75,730 (42.72)	104 (81.89)	57,536 (37.30)	101 (73.19)	161,641 (31.72)	271 (76.34)
Pharmacist	9883 (5.55)	2 (2.22)	18,862 (10.64)	3 (2.36)	16,422 (10.65)	1 (0.72)	45,167 (8.86)	6 (1.69)
Other Health Professional	33,238 (18.67)	14 (15.56)	28,999 (16.36)	11 (8.66)	22,429 (14.54)	26 (18.84)	84,666 (16.62)	51 (14.37)
Lawyer	14,080 (7.91)	0 (0.00)	780 (0.44)	1 (0.79)	173 (0.11)	0 (0.00)	15,033 (2.95)	1 (0.28)
Consumer/Non Health Professional	3415 (1.92)	6 (6.67)	41,253 (23.27)	6 (4.72)	16,317 (10.58)	9 (6.52)	60,985 (11.97)	21 (5.92)
Unknown	89,052 (50.02)	2 (2.22)	11,661 (6.58)	2 (1.57)	41,357 (26.81)	1 (0.72)	142,070 (27.88)	5 (1.41)

ADR—adverse drug reaction. * Monte Carlo simulation (CI: 99%, based on 10,000 sampled tables with a starting seed of 2,000,000). ** Fisher–Freeman–Halton Exact Test. While statistically significant differences were observed ($p < 0.05$), the effect size (Cohen's w-values) indicates a small practical difference with limited clinical significance.

2.1.2. Anemia

In all five reporting structure categories (patient age, sex, whether the ADR was serious or not, the seriousness criteria, and the reporter's qualification), significant differences were found between World and Serbia ($p < 0.05$). Most reported cases were serious, reported by physicians, and in female patients aged 45–64 years. Globally, most of the reported cases caused/prolonged hospitalization (44.92%), while in Serbia, they were classified as "other medically important condition" (53.49%). Pharmacists reported 10.64% of cases in World, compared to 2.36% in Serbia. Detailed results are presented in Table 1 and the Supplementary File.

2.1.3. Thrombocytopenia

In both World and Serbia, the majority of reported cases were categorized as serious (>78%) and were in the category "other medically important condition". Thrombocytopenia was mostly reported in patients in the 45–64 year age group. In Serbia, the majority were female (54.76%), contrasting World, where a higher number of reports were in male patients (49.92%). Additionally, in Serbia, 73.19% were reported by physicians, whereas in World, this figure was 37.30%. The difference in reporter qualification is noticeable when comparing World and Serbia: almost 15 times higher in World compared to Serbia for cases

reported by pharmacists, at 10.65% vs. 0.72%, respectively. Other results are presented in Table 1 and the Supplementary File.

2.1.4. Cytopenias in Total

Overall, cytopenias were mostly reported in female patients aged 45–64 years. In Serbia, the number of reported cases in female patients is ~10% higher than the globally (61.61% vs. 51.34%). The difference in reported cases between World and Serbia is even more noticeable for serious cases (80.65% vs. 67.72%) and especially in the seriousness criteria for the category "other medically important condition" (60.68% vs. 46.88%). The number of reported cases by physicians represents 76.34% of the total reported cases in Serbia, whereas in World, this proportion is significantly lower at 31.72% ($p < 0.05$).

2.2. Adverse Reaction Reporting Rate

Reporting rates were the highest for leucopenia, both in World and in Serbia. Globally, the number of drug-induced anemia cases was higher than that for thrombocytopenia, while in Serbia, it was the opposite. Results are presented in Table 2.

Table 2. Reporting rates for all cytopenia types (2014–2023). Reporting rates are expressed as ADR/million/year.

ADR Type	Area	Average	Standard Deviation	Maximum	Minimum	Median	95% CI [Lower–Upper Limits]
LEUCOPENIA	Global	0.96	0.27	1.49	0.55	1.03	0.20 [0.77–1.16]
	Serbia	1.26	0.55	2.28	0.58	1.20	0.39 [0.87–1.66]
ANEMIA	Global	2.09	0.35	2.71	1.78	2.02	0.25 [1.84–2.34]
	Serbia	1.75	0.82	3.09	0.84	1.44	0.58 [1.17–2.34]
THROMBOCYTOPENIA	Global	1.82	0.53	2.69	1.05	1.73	0.38 [1.44–2.20]
	Serbia	1.81	0.70	3.24	0.97	1.52	0.50 [1.31–2.31]
TOTAL CYTOPENIA	Global	4.87	0.63	5.70	3.53	4.85	0.45 [4.42–5.32]
	Serbia	4.83	1.70	8.39	2.95	4.32	1.22 [3.61–6.04]

ADR—adverse drug reaction; CI—confidence interval.

2.2.1. Leucopenia

The average reporting rate for leucopenia in World over the 10-year period was 0.96 ± 0.27 (0.55–1.49) ADR/million/year, while in Serbia, it was 1.26 ± 0.55 (0.58–2.28) ADR/million/year. Comparable RRs were observed in 2016, 2017, and 2019. In 7 out of 10 years, a higher RR was observed in Serbia. All results for the period 2014–2023 are provided in Figure 1A.

2.2.2. Anemia

The average RR for anemia was higher in World compared to the rate observed in Serbia (average: 2.09 vs. 1.75 ADR/million/year). Globally, the highest RR was recorded in 2014 (2.71 ADR/million/year), while in Serbia, it was in 2022 (3.09 ADR/million/year). Conversely, the lowest RR in World was observed in 2020, while in Serbia, it was reported in 2016 (1.78 vs. 0.84 ADR/million/year, respectively). Figure 1B shows the anemia RR for World and for Serbia.

2.2.3. Thrombocytopenia

For thrombocytopenia, the average RRs of World and Serbia are comparable, at 1.82 vs. 1.81 ADR/million/year. During the observed period, their RRs ranged from 0.97 to 3.24 ADR/million/year for Serbia and from 1.05 to 2.69 globally. All thrombocytopenia reporting rates are presented in Figure 1C.

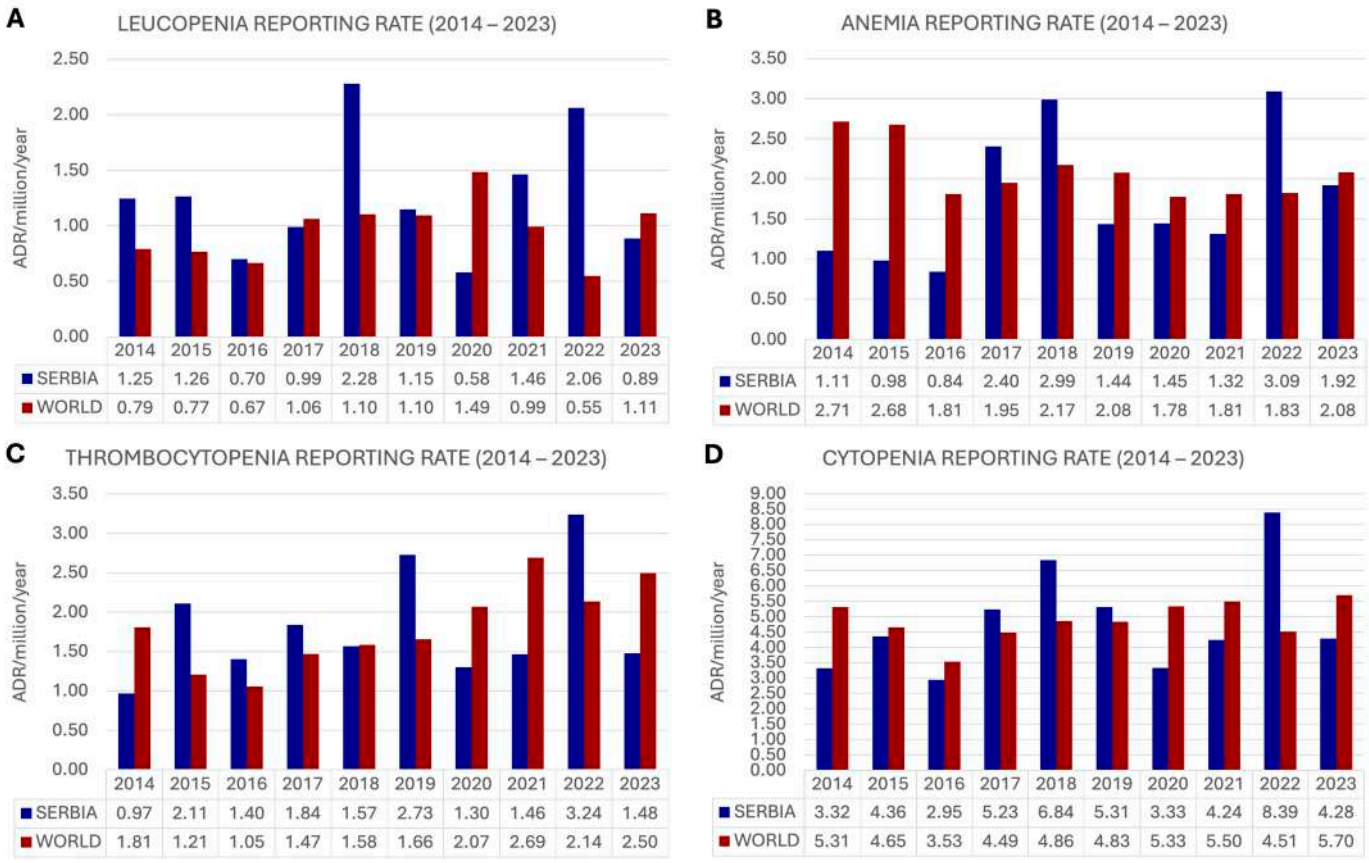

Figure 1. Reporting of drug-induced cytopenias from 2014 to 2023. ADR—adverse drug reaction. (**A**) Leucopenia; (**B**) Anemia; (**C**) Thrombocytopenia; (**D**) Total cytopenia.

2.2.4. Cytopenia in Total

The reporting rate (Figure 1D) for cytopenia ranged from 2.95 ADR/million/year to 8.39 ADR/million/year in Serbia, while globally, the RR range was from 3.53 to 5.70 ADR/million/year. The average RR in World (4.87 ± 0.63, 3.53–5.70) and Serbia (4.83 ± 1.70, 2.95–8.39) over the 10-year period was comparable.

2.3. Adverse Reaction Reporting Trend

An increasing trend in the reporting of all types of DICs is observed in Serbia over a ten-year period, while in World, this trend is only evident for leucopenia. Figure 2 shows joinpoints, i.e., the points where changes in direction are observed. The variability in reporting is higher in Serbia, suggesting inconsistent pharmacovigilance practices. In the Supplementary File, additional details on trend segments and APC (annual percentage change) are provided.

2.3.1. Leucopenia

Over the 10-year period, the analysis of leucopenia cases reported in World and in Serbia, expressed as ADR/million/year, showed no statistically significant change in trend ($p > 0.05$), as both showed an increase in reporting. From Figure 2, it can be seen that the growth in reporting trend was around 2 times higher in World.

The coefficient of unalikeability is greater for Serbia, indicating higher variability in the percentage change in leucopenia reporting over the years. The results are presented in Table 3.

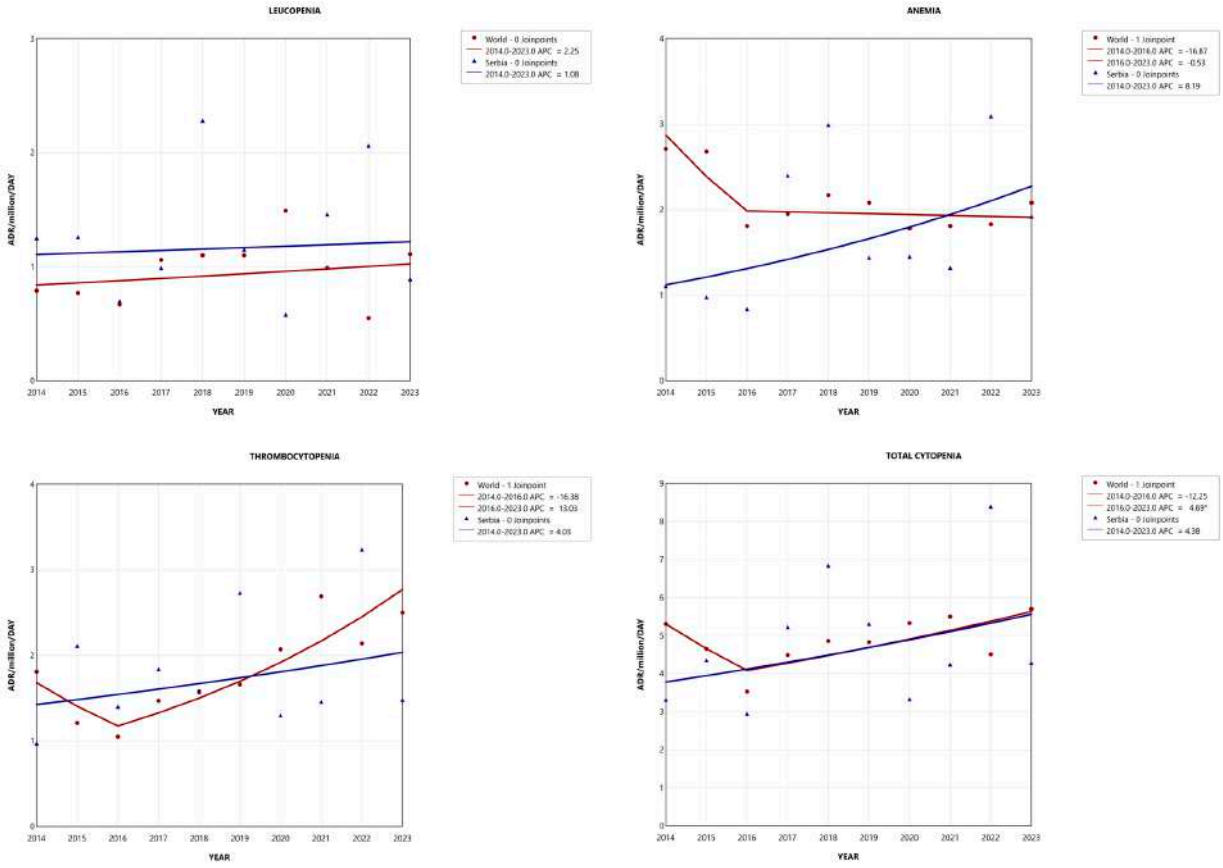

Figure 2. Reporting trends in drug-induced cytopenias from 2014 to 2023. ADR—adverse drug reaction; APC—annual percentage change. * Indicates that the APC is significantly different from zero at alpha = 0.05 level.

Table 3. Coefficient of unalikeability for ADR reporting rates for 2014–2023.

Criteria for Unalikeability Difference *	Area	Leucopenia	Anemia	Thrombocytopenia	Total Cytopenia
≥10%	World	0.40	0.32	0.44	0.28
	Serbia	0.46	0.46	0.43	0.44
≥15%	World	0.37	0.24	0.40	0.22
	Serbia	0.41	0.43	0.38	0.42
≥20%	World	0.34	0.18	0.34	0.12
	Serbia	0.40	0.41	0.34	0.36
≥25%	World	0.31	0.13	0.29	0.08
	Serbia	0.34	0.34	0.31	0.26
≥30%	World	0.20	0.11	0.23	0.04
	Serbia	0.30	0.32	0.27	0.26
≥35%	World	0.13	0.02	0.18	0.02
	Serbia	0.28	0.29	0.19	0.22
≥40%	World	0.09	0.01	0.14	0.00
	Serbia	0.22	0.24	0.17	0.12
≥45%	World	0.08	0.01	0.08	0.00
	Serbia	0.17	0.20	0.14	0.10
≥50%	World	0.04	0.00	0.06	0.00
	Serbia	0.13	0.18	0.10	0.07

* The coefficient of unalikeability is calculated for different % changes in reporting rates of ADRs between any two years; if the difference between years was greater than or equal to the stated %, it was transformed to 1; otherwise, it was transformed to 0. ADR—adverse drug reaction.

2.3.2. Anemia

Globally, the reporting trend of anemia cases showed a non-significant decrease from 2014 to 2016, with an APC of −16.87 ($p > 0.05$), and from 2016 to 2023, there was almost no change (APC = −0.53, $p > 0.05$). On the other hand, in Serbia, during this 10-year period, a continuous increase is observed throughout the reporting period, but there was also no significant change (APC = 8.19, $p > 0.05$).

The number of anemia cases reported in Serbia varied more across years; detailed information on variability is provided in Table 3.

2.3.3. Thrombocytopenia

The reporting trend for thrombocytopenia showed an increase in Serbia throughout the entire observed period (APC = 4.03, $p > 0.05$). Globally, there was an increase in reported cases of thrombocytopenia from 2016 (APC = 13.03, $p > 0.05$).

The stability of the reporting process for thrombocytopenia is comparable between World and Serbia, for a 10% change in RR between years. Results for variability between years (10–50%) are presented in Table 3.

2.3.4. Cytopenia in Total

The trend for the total number of cytopenia cases reported indicated an APC increase of 4.38 ($p > 0.05$) in Serbia, whereas in World, there was one joinpoint in 2016. Globally, there was a decrease before 2016 (APC = −12.25, $p > 0.05$), while an increase was seen after 2016 (APC = 4.69, $p < 0.05$). Based on Figure 2, the reporting trend for total cytopenia has been comparable between the world and Serbia since 2016.

Greater variability in the percentage change in total cytopenia reporting is observed for Serbia. In World, variability in RR between years is less than 40%, and other results are in Table 3.

3. Discussion

A comparison of reported cases of DIC in World and in Serbia showed that there are certain differences, specifically in the reporting of leucopenia, which is reported more often in Serbia. This is mainly because physicians are more represented as reporters and, in principle, encounter serious leucopenia often in their daily work, increasing the frequency of reports of serious leucopenia. Globally, drug-induced anemia often leads to or prolongs hospitalization, in contrast to other types of cytopenias, which most often result in "other medically important condition", both in World and in Serbia. In Serbia, regardless of the type of cytopenia, there has been a constant increase in reporting during the observed period. On the other hand, globally, this refers to reporting leucopenia cases, while for other types of cytopenias, a joinpoint was observed, where a decrease in anemia cases has been seen in recent years. Our results show that the stability of the reporting process is higher in World, as evidenced by changes in RR percentages between years, which are lower in different types of cytopenias.

Discrepancies exist in the suspected substances reported to causes of DIC. This is not surprising, given that there are also discrepancies in treatment protocol, guidelines, accessibility, and affordability of drugs between countries. Leucopenia and thrombocytopenia were mostly reported for drugs indicated in oncology, in both World and Serbia, while for anemia, there are differences not only in substances (e.g., only furosemide is most commonly reported in both World and Serbia) but also in therapeutic groups. Regardless of the type of cytopenia and whether it is reported globally or in Serbia, the majority of cases reported occurred in women (up to 66%), except for thrombocytopenia, which was reported in 44% of females in World. These results are consistent with other publications

in which the number of reported ADRs was higher in females [27–37]. Our result is not surprising, given that women also predominate in reports of other ADRs, possibly because they have a higher risk of developing ADRs, as shown by Rademaker [38].

For all types of analyzed cytopenias (World and Serbia), most patients were of working age, which is consistent with the results of other publications [27,29,34]. In contrast, the studies by Jiang et al. and Dubrall et al. reported the largest number of cases in patients older than 65 years [28,32]. This result is probably due to the correlation between age, the number of prescribed medications, and ADR reporting rates [39,40].

In Serbia, most cases involving any type of cytopenia, as well as total cytopenias, were reported by physicians, which aligns with other publications [32,35,36]. Globally, all types of cytopenias except leucopenia were also mostly reported by physicians; cases of leucopenia were most often reported by other healthcare workers. Pharmacists are also recognized as healthcare professionals and, depending on the healthcare system, can report ADRs [30,33,41]. In Serbia, reporting of both, all types of ADRs and DICs, comes predominantly from physicians (~60% and ~76%, respectively), while in the case of cytopenia, reporting by pharmacists is lower compared to reporting of all types of ADRs (1.69% versus 33.8%, respectively) [42]. Most reports of DICs from physicians primarily refer to patients who are already hospitalized, as they undergo more frequent blood testing, concomitantly receive more medications, and are closely monitored compared to those who are not hospitalized [43–46]. Since access to the laboratory values of patients' results, or the ordering of laboratory analyses by pharmacists, is limited and varies between countries, it is expected that the number of reports of cytopenia as an ADR by pharmacists or patients is lower compared to that of other types of ADRs [47]. Increasing access to laboratory results for pharmacists would probably improve this situation and increase recognition and DIC reporting, as different studies imply that pharmacists' access to laboratory results and pharmacists' inclusion in chronic disease management lead to fewer drug-related problems, better adherence, better quality of patient care, and improved management of chronic diseases such as chronic obstructive pulmonary disease (COPD) and diabetes. In Canada, one study found that 87% of pharmacists with access to laboratory results reported better quality of care. On the other hand, Al Hamarneh et al. showed the potential contribution of pharmacists having access to laboratory results to the diagnosis of chronic diseases, with results indicating that previously undiagnosed chronic kidney diseases were detected in 40% of patients considered high risk [47–50].

Cases of ADRs characterized as serious accounted for more than 50% of reports, both globally and in Serbia, for anemia, thrombocytopenia, and total cytopenia. When reporting drug-induced leucopenia, in Serbia, 78% of cases were categorized as serious, while globally, it was less than 50%. Studies show variability in the seriousness of the different types of ADRs reported, where more than 50% of ADRs were reported as serious in some cases [32,33], while in others, less than 50% were serious [30,34,37,51]. According to the Food and Drug Administration Adverse Event Reporting System (FAERS) database, the number of reports characterized as serious is 55.17% (cut-off date: 31 March 2025) [52]. For cytopenia, more cases are reported as serious because less serious blood count disorders are very common and are often resolved without consequences; they do not paint a clear clinical picture that requires therapy or intervention from a healthcare worker, so they are often unrecognized [20,53].

Globally, the serious criterion in most reported cases was "other medically important condition" (up to 66%), except for cases of anemia, in which it was "caused/prolonged hospitalization". It is interesting that cases of "death" varied from 4% to 7%, which is in line with other publications that refer to this category when reporting all types of ADRs [28,36];

however, according to the FAERS database, the proportion of "death cases" is a slightly higher (~9%) [52].

The RR is generally low both in World and in Serbia, which is not surprising since underreporting is recognized as a major challenge in real-world practices for all types of ADRs [20–22,54]. According to Stevic et al., who analyzed the costs of DICs, if the number of cases per year is compared, it can be seen that the number of cases is many times higher than the number of total annual reports for cytopenia (e.g., in Serbia, during a three-year period, 71 cases of drug-induced anemia were discovered in only one tertiary healthcare hospital after reviewing patient files, while there were only 40 reports to the National Pharmacovigilance Centre) [42,55].

The difference in RR between World and Serbia, as well as within each group, has varied over the observed period. Leucopenia and total cytopenia RRs were greater in Serbia, in contrast to anemia. For thrombocytopenia, the RR differed between years, where the RR was higher in an equal number (five) of years (in the world and in Serbia). These variations probably arise due to the variability in underreporting, which varies over time. With improved recognition of DIC and responsible reporting, these trends would probably be quite different. Additionally, it is worth noting that there are noticeable differences between countries also in treatment guidelines, the availability and accessibility of various drugs, recommendations in drug policies, and the level of reporter knowledge about pharmacovigilance and ADR reporting, which may also influence the variability in reporting [56–59].

Limitations of the Study

Limitations and data quality related to VigiBase are also applicable to our data (e.g., suspected cases included, variation in strength of causality, heterogeneity of data, etc.) [60,61]. The analysis is limited to data from one database of spontaneous reports, where the number of cytopenia cases reported globally is compared to only one country, and due to differences in sample sizes, the effect size may indicate a small practical difference with limited clinical significance. Additionally, due to limited access to data in publicly available databases, which refer to ADR reports by drug/active substance rather than by the type of ADR, it was not possible to perform comparisons across different regions and continents.

Also, the number and type of variables present in the databases are limited, so it was not possible to analyze the causality of those differences in RR and trends, as well as the effect of confounding factors, access to healthcare, patterns of drug exposure, main drug indication, and healthcare utilization among different populations.

It should not be forgotten that the database primarily contains reports of suspected ADRs for which causality with the reported drug has not been established with certainty, so the observed trends and RRs do not reflect the actual occurrence of DIC and include reports that are subject to many factors that often cannot be identified in this type of analysis (changes in health policy, economic situation in the country, emergency situations such as COVID-19, etc.). Finally, there are differences in the age distribution of different populations, which could affect drug utilization and the number of ADRs, but this was not taken into account in this study; i.e., unlike the incidence or prevalence of a disease, reporting of ADRs does not have to be age-specific. Age standardization and systematic ascertainment bias were not considered in this type of analysis. The descriptive nature of this analysis, utilizing spontaneous reporting data, precludes the calculation of true incidence or the establishment of definitive causal relationships.

4. Materials and Methods

This research was designed as a secondary study based on data from spontaneously reported ADRs from the World Health Organization (WHO) global database of individual case safety reports (ICSRs)—VigiBase (VigiBase, the WHO global database of reported adverse events of medicinal products; information comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases (causal relationships between the event and a medicine or vaccine may be difficult to establish due to limitations in the data); information and any results and conclusions drawn do not represent the opinions of the Uppsala Monitoring Centre (UMC), the WHO Collaborating Centre for International Drug Monitoring, or the World Health Organization) [60,61]. From VigiBase, researchers from the National Pharmacovigilance Centre in Serbia independently extracted data, following data policy, on a yearly basis for the 10-year period (2014–2023) separately for the reported cases globally (referred as "World") and for Serbia. Extracted data included the total number of case reports for leucopenia, anemia, and thrombocytopenia. Additionally, for reported cases, data were collected on the structure (distribution of ADR report cases among categories) of these cases, including patient age, sex by birth, whether the ADR was serious or not, the seriousness criteria, and the reporter's qualification. Also, data on the 10 most commonly reported drugs (at the international non-proprietary name (INN) level) related to each cytopenia type were collected for each year. No additional inclusion/exclusion criteria were applied; the quality of the data, as well as its limitations, follows those related to VigiBase, as outlined in the caveat document and the guideline for using VigiBase data [60,61]. Reporting structure categories were for (i) age: 0–27 days, 28 days to 23 months, 2–11 years, 12–17 years, 18–44 years, 45–64 years, 65–74 years, more than 75 years, and unknown; (ii) sex by birth categories: female, male, and unknown; (iii) if the ADR is categorized as serious: yes, no, and unknown; (iv) the seriousness criteria: death, life-threatening, caused/prolonged hospitalization, disabling/incapacitating, congenital anomaly/birth defect, and other medically important conditions; and (v) the reporter's qualification categories: physician, pharmacist, other health professionals, lawyer, consumer/non health professional, and unknown.

Based on the extracted data, IS compiled them and created datasets for leucopenia, anemia, and thrombocytopenia. Additionally, a dataset for total cytopenia was created by combining all aggregated datasets for World and for Serbia. The quality of compilation of the final dataset was independently assessed by the second researcher, SJ. Since data were not extracted at the individual patient level, but rather at the yearly level for all reports in World and Serbia, there was no coding of the data, except for coding Serbia and the World as variables.

Descriptive statistics were performed, and they included a description of the reporting structure for each cytopenia type and for total cytopenia, which was expressed as the number of reported cases (N), as well as a proportion of specific categories in the total number of reported cases (%), and it was analyzed using Microsoft Office Excel for Mac ver 16.75.

Differences in the structure of reported cases between World and Serbia were determined using the chi-square test (including Monte Carlo simulations and Fisher–Freeman–Halton Exact Test) in IBM SPSS for Mac version 29 [62]. The results were considered significant if the probability of the null hypothesis (p) was less than 0.05.

Data on the total number of annual reported cases for leucopenia, anemia, thrombocytopenia, and total cytopenia in World and in Serbia were used to calculate the annual reporting rate. The RR was calculated and expressed as the number of reports per 1,000,000 inhabitants per year (referred in the text as ADR/million/year). For each year, the number of inhabitants in World and in Serbia used for calculation was obtained from relevant sources [63,64].

The trend analysis, based on the reporting rate (ADR/million/year), was conducted using the joinpoint regression method, which identifies the trends between points (years) where the intensity or direction of change occurs, along with the calculation of the annual percentage change (APC). Joinpoint software version 5.4 was used to perform this analysis [65]. To evaluate the variability in reporting between years, that is, to examine the stability of the reporting process and not just the reporting trend, we also calculated the coefficient of unalikeability, where we used the degree of variability between any two years (from 10% to 50%) and assigned the categories 0 and 1 (if the difference between years was greater than or equal to the stated %, it was transformed to 1; otherwise, it was transformed to 0) [66].

5. Conclusions

Cytopenias are adverse drug reactions in which the clinical picture develops relatively late compared to the effect of noxa (noxae). they can also have a large number of other causes, which complicates their identification as a drug-induced disorder and thus cytopenia reporting. Although efforts are being made to increase reporting of drug-induced cytopenias, as confirmed by the upward trends revealed in our work, additional research is needed. In particular, it is important to investigate whether healthcare professionals and patients recognize adverse reactions detected through laboratory blood testing, such as cytopenias, as adverse reactions, as this would facilitate work on education and raising awareness about the importance of reporting adverse reactions. Additionally, future studies should investigate the impact of confounders (e.g., age, sex, and drug class) on reporting trends of DIC, DIC reporting for a particular drug or drug class, the causes of inconsistent pharmacovigilance practices, multinational comparisons, and the usage of causality tools and interventions to improve the reporting of ADRs. Many measures are needed, which should focus on promoting the early detection of cytopenias, primarily by increasing access to blood count results for all healthcare professionals, including pharmacists.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ph19010014/s1, Table S1: Reporting structure for leucopenia, anemia, thrombocytopenia, and cytopenia in total (2014–2023) in the World and Serbia. Table S2: Trend segments, Annual Percent Change with 95% lower and upper limits with significance of the trend segments.

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УНИВЕРЗИТЕТ У БЕОГРАДУ
ФАРМАЦЕУТСКИ ФАКУЛТЕТ
Војводе Степе 450
11000 Београд
Посл.број: 2956/2
Датум: 24.12.2024.

На основу члана 19. Правилника о раду Етичког комитета за биомедицинска истраживања Фармацеутског факултета у Београду, Етички комитет за биомедицинска истраживања Фармацеутског факултета у Београду на седници одржаној 23.12.2024. године, донео је

О Д Л У К У

ДАЈЕ СЕ САГЛАСНОСТ за спровођење истраживања под називом: „Фармакоепидемиолошки и фармакоекономски аспекти цитопенија узрокованих применом лекова“ у циљу израде докторске дисертације.

Ментори докторске дисертације су проф. др Валентина Маринковић, редовни професор на Катедри за споцијалну фармацију и фармацеутско законодавство, Универзитета у Београду-Фармацеутског факултета и проф. др Драгана Лакић, ванредни професор на Катедри за социјалну фармацију и фармацеутско законодавство Фармацеутског факултета - Универзитета у Београду.

Молбу за давање сагласности поднела је спец. Ивана Стевић, докторант на докторским академским студијама на Фармацеутском факултету Универзитета у Београду - модул Социјална фармација и истраживање фармацеутске праксе

Одлуку доставити: подносиоцу захтева, менторима, председнику Комитета, секретару, шефу Одсека за правне и опште послове, Одсеку за наставу и студентска питања и Архиви.

ПРЕДСЕДНИК ЕТИЧКОГ КОМИТЕТА
ЗА БИОМЕДИЦИНСКА ИСТРАЖИВАЊА

Проф. др Александра Стефановић

UNIVERSITY CLINICAL CENTER KRAGUJEVAC

УНИВЕРЗИТЕТСКИ КЛИНИЧКИ ЦЕНТАР КРАГУЈЕВАЦ

ODLUKA ETIČKOG ODBORA

NAZIV I ADRESA ETIČKOG ODBORA: UKC Kragujevac, ul. Zmaj Jovina 30, 34000 Kragujevac
NAZIV STUDIJE:**„Ispitivanje troškova lečenja i ekonomska evaluacija lečenja hematoloških poremećaja uzrokovanih primenom lekova.“**
VERZIJA I DATUM PROTOKOLA:Studija bez broja protokola, dokumentacija zavedena u pisarnici UKC Kragujevac sa brojem 01/22/308 dana 21.09.2022.g.
NAZIV I ADRESA SPONZORA: Sponzor ne postoji
IME I ADRESA GLAVNOG ISTRAŽIVAČA: prof.dr Slobodan Janković, Služba za kliničku farmakologiju, UKC Kragujevac, ul.Zmaj Jovina 30, Kragujevac 34000
PREGLEDAN MATERIJAL
Sledeći dokumenti u vezi gore navedene studije koju će sprovesti navedeni istraživač su pregledani na sednici od 05.10.2022 .godine: 1. Protokol ispitivanja 2.Sažetak protokola 3.Izjavu o etičkim dokumentima kojh se protokol pridržava 4. Izjava istraživača o saglasnosti sa protokolom ispitivanja 5.Biografije svih istraživača (datirane i potpisane) 6.Izjava o bilo kom obliku nadoknade pacijentima za učešće u studiji 7.Izjava o načinu nadoknade eventualne štete 8.Opis osiguranja pacijenata 9.Saglasnost direktora Organizacione jedinice gde se studija sprovodi
Zaključak: ODOBRENA SU PREGLEDANA DOKUMENTA
Datum zasedanja:05.10.2022 .godine Predsednik Etičkog odbora Prof dr Vladimir Janjić Odobrenje važi za vreme trajanja studije, ako drugačije nije navedeno. **Etički odbor UKC-a Kragujevac se u svom radu pridržava smernica ICH GCP.**
ČLANOVI ETIČKOG ODBORA UKC KRAGUJEVAC
1. Prof dr Vladimir Janjić — predsenik **2. Prof.dr Tatjana Šarenac — zamenik predsednika** **3. Doc.dr Dejana Ružić Zečević — član** **4. Doc.dr Branimir Radmanović — član** **5. Doc.dr Tatjana Bošković Matić — član** **6. Prof.drTatjana Vulović — član** **7. Dr Raša Medović — član**

Na sednici Etičkog odbora od 05.10.2022 . godine, kada su razmatrana gore navedena dokumenta, prisustvovali su svi člnovi Etičkog odbora. Svi prisutni članovi su jednoglasno odobrili podneta dokumenta.

Datum zasedanja: 05.10.2022 godine

Predsednik Etičkog odbora
Prof dr Vladimir Janjić

Subject: RE: Сагласност
Date: Tuesday, 24 March 2026 at 13:43:20 Central European Standard Time
From: Ivana Jović
To: Valentina Marinković
CC: Marija Mihailović, Ivana Stević

Poštovana profesorka,

Budući da je Agencija za lekove i medicinska sredstva Srbije dostavila podatke za pripremu publikacije "*Cytopenias as Adverse Drug Reactions: A 10-Year Analysis of Reporting Structure, Rate, and Trend*", isti podaci se mogu koristiti za izradu doktorske disertacije koleginice Ivane Stević.

Srdačan pozdrav,
Ivana

Mr ph. spec. Ivana Jović

Nacionalni centar za farmakovigilancu
Centar za humane lekove
Agencija za lekove i medicinska sredstva Srbije
Vojvode Stepe 458, 11 221 Beograd
Telefon/Fax: (+381 11) 3951 130

From: Valentina Marinković <valentina.marinkovic@pharmacy.bg.ac.rs>
Sent: 24. mart 2026 9:20
To: Ivana Jović <ivana.jovic@alims.gov.rs>
Cc: Marija Mihailović <marija.mihailovic@alims.gov.rs>; Ivana Stević <ivana.stevic@pharmacy.bg.ac.rs>
Subject: Сагласност

Поштована Ивана,

Надам се да сте добро!
Потребна нам је формална сагласност АЛИМС-а да податке који су коришћени за израду публикације "*Cytopenias as Adverse Drug Reactions: A 10-Year Analysis of Reporting Structure, Rate, and Trend*" где сте и Ви и колегиница Марија Михаиловић ко-аутори рада, а који је објављен у часопису *Pharmaceuticals,* колегиница Ивана Стевић може да користи за израду докторске дисертације под називом "Фармакоепидемиолошки и фармакоекономски аспекти цитопенија узрокованих применом лекова".

Унапред хвала.
Срдачно
Валентина

Valentina Marinković, PhD

Full Professor

Department of Social Pharmacy and Pharmaceutical Legislation
Faculty of Pharmacy, University of Belgrade
Vojvode Stepe 450
11000 Belgrade
SERBIA

tel. +381 11 3951285
http://www.pharmacy.bg.ac.rs/o-fakultetu/redovni-profesori/729/dr-sc-valentina-marinkovi%C4%87/

УНИВЕРЗИТЕТ У БЕОГРАДУ
ФАРМАЦЕУТСКИ ФАКУЛТЕТ
Посл.број: 3/96
29.10.2025. године

На основу члана 107. Закона о високом образовању Републике Србије, продекан за последипломску наставу и континуирну едукацију Факултета је дана 29.10.2025. године, донела

Р Е Ш Е Њ Е

ОДОБРАВА се СТЕВИЋ ИВАНИ, студенту Фармацеутског факултета, индекс бр. **26/2018**, **продужетак рока за завршетак студија у школској 2025/2026. години.**

О б р а з л о ж е њ е

СТЕВИЋ ИВАНА, студент на **ДАС – Социјална фармација и истраживање фармацеутске праксе**, поднела је захтев број 3/96 од 29.10.2025. године продекану за последипломску наставу и континуирану едукацију Факултета да јој се одобри продужетак рока за завршетак студија.

Уз молбу је приложила одговарајућу документацију.

Продекан Факултета је разматрала захтев 29.10.2025. године и оценила да је захтев основан, те је донето решење као у диспозитиву.

ПРАВНА ПОУКА: Против овог решења именовани има право приговора декану Факултета у року од 8 (осам) дана од дана пријема истог.

Решење доставити: Именованом студенту, Одсеку за наставу и студентска питања.

ПРОДЕКАН ЗА ПОСЛЕДИПЛОМСКУ
НАСТАВУ И КОНТИНУИРАНУ
ЕДУКАЦИЈУ

Проф. др Душанка Крајновић

УНИВЕРЗИТЕТ У БЕОГРАДУ
ФАРМАЦЕУТСКИ ФАКУЛТЕТ
Посл.број:3/104-1
Дана 20.09.2021.године

На основу члана 107. Закона о високом образовању Републике Србије, продекан Факултета је дана 20.09.2021. године, донела

Р Е Ш Е Њ Е

ОДОБРАВА се ИВАНИ СТЕВИЋ, студенту Фармацеутског факултета, индекс бр. **26/2018**, **мировање права и обавеза студента у школској 2021/2022 години.**

О б р а з л о ж е њ е

ИВАНА СТЕВИЋ, студент на студијском програму **ДАС – Социјална фармација и истраживање фармацеутске праксе**, поднела је захтев бр. 3/104-1 од 20.09.2023. године продекану за последипломске студије Факултета да јој се одобри **мировање права и обавеза студента у школској 2021/2022 години.**

Продекан Факултета је разматрала захтев 20.09.2021. године и оценила да је захтев основан, те је донето решење као у диспозитиву.

ПРАВНА ПОУКА: Против овог решења именовани има право приговора декану Факултета у року од 8 (осам) дана од дана пријема истог.

Решење доставити: Именованом, декану, продекану за наставу, секретару, Одсеку за наставу и студентска питања и архиви.

ПРОДЕКАН ЗА ПОСЛЕДИПЛОМСКУ НАСТАВУ
И КОНТИНУИРАНУ ЕДУКАЦИЈУ

Проф. др Сандра Везмар Ковачевић