

Evaluation of Preclinical and Clinical Studies Published in Medical Journals of Bosnia and Herzegovina: Methodology Issues

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ABSTRACT

Introduction: Results of preclinical and clinical studies in medicine could be trusted only if their design and statistical analysis were appropriate. **Aim:** The aim of our study was to investigate whether preclinical and clinical studies published in medical journals of Bosnia and Herzegovina satisfy basic requirements for appropriate design and statistical interpretation of data. **Methods:** Preclinical and clinical studies published in medical journals of Bosnia and Herzegovina were retrieved from the PubMed database, and the sample for analysis was randomly chosen from the retrieved publications. Implementation rate of basic principles of experimental design (local control, randomization and replication) and rate of the most common errors in design of clinical/observational studies was established by careful reading of the sampled publications and their checking against predefined criteria. **Results:** Our study showed that only a minority of experimental preclinical studies had basic principles of design completely implemented (7%), while implementation rate of single aspects of appropriate experimental design varied from as low as 12% to as high as 77%. Only one of the clinical/observational studies had none of the errors searched for (2%), and specific errors rates varied from 10% to 89%. Average impact factor of the surveyed studies was around one, and average publication date recent, less than 5 years ago. **Conclusion:** Prevalence of preclinical studies that did not follow completely basic principles of research design, and that of clinical/observational studies with errors are high, raising suspicion to validity of their results. If incorrect and not protected against bias, results of published studies may adversely influence future research.

Keywords: randomization; control experiments; replication; internal validity; errors; bias.

1. INTRODUCTION

If not designed and conducted appropriately, both preclinical and clinical/observational studies in medicine will produce incorrect results and erroneous conclusions, misleading future researchers who will use them as basis for their own studies. (1). There are several ways to prevent errors in research design, e.g. establishing guidelines for preclinical and clinical/observational studies (2), teaching research design at under- or post-graduate studies (3), and publishing special methodological articles in medical journals. However, surveys showed that more than half of the studies published in medical journals had some er-

rors in design making their conclusions questionable (4). While for preclinical studies it is important to satisfy three basic principles of design (having appropriate negative and positive controls, replicating experiments on independent experimental units and random assignment of a treatment and an alternative to experimental units) (5), clinical and observational studies should avoid measuring bias, should be conducted on a sample of sufficient size, their statistics should be based on correct assumptions and their limitations should be openly and honestly stated. Failure to acknowledge and implement these principles when designing a study will

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lead to production of incorrect or spurious results, and real truth about the object of study will remain hidden (6). In our recent research on representative sample of experimental studies indexed in PubMed we have revealed that only a handful of studies (7%) were methodologically excellent, while majority had serious problems with design (7).

2. AIM

The aim of our study was to investigate whether preclinical and clinical/observational studies published in medical journals of Bosnia and Herzegovina (B&H) satisfy basic requirements for appropriate design and statistical interpretation of data.

3. METHODS

The studies were retrieved for analysis from the PubMed database. For the preclinical studies, the following inclusion criteria defined the pool from which the study sample was extracted: journal article, published in a journal issued in Bosnia and Herzegovina, original experimental study, animal study, in vitro study and full text availability. The exclusion criteria were: review articles, clinical trials of phase I-IV, cohort studies, case control studies and cross-sectional studies. The following search strategy was used to implement inclusion and exclusion criteria and select the pool of preclinical studies for further analysis: ((“acta informatica medica”) AND ((animal study) OR (in vitro study))) OR ((“materia socio-medica”) AND ((animal study) OR (in vitro study))) OR ((“medical archives”) AND ((animal study) OR (in vitro study))) OR ((“acta medica academica”) AND ((animal study) OR (in vitro study))) OR ((“medicinski glasnik”) AND ((animal study) OR (in vitro study))) OR ((“bosnian journal of basic medical sciences”) AND ((animal study) OR (in vitro study))). Filter Free Full text.

For the clinical and observational studies, the following inclusion criteria defined the pool from which the study sample was extracted: journal article, published in a journal issued in Bosnia and Herzegovina, original clinical trial, original observational clinical study, and full text availability. The exclusion criteria were: review articles, animal studies, in vitro studies, modelling studies and case reports or case series. The following search strategy was used to implement inclusion and exclusion criteria and select the pool of clinical/observational studies for further analysis: ((“acta informatica medica”) AND ((observational study) OR (clinical trial))) OR ((“materia socio-medica”) AND ((observational study) OR (clinical trial))) OR ((“medical archives”) AND ((observational study) OR (clinical trial))) OR ((“acta medica academica”) AND ((observational study) OR (clinical trial))) OR ((“medicinski glasnik”) AND ((observational study) OR (clinical trial))) OR ((“bosnian journal of basic medical sciences”) AND ((observational study) OR (clinical trial))). Filters: Free full text.

Size of the study sample for both preclinical and clinical/observational studies (n=43) was calculated

on the basis of the following assumptions: rate of inappropriate research design 0.5 (4) and width of the 95% confidence interval ± 0.15 . The formula $n = (1.96)^2 \times 4 \cdot p \cdot (1-p) / d^2$ was used for the calculation, where „n“ is the sample size, „p“ probability of inappropriate research design and „d“ width of the confidence interval (8). Since the studies retrieved by the abovementioned search strategy were numbered orderly in the PubMed database, the study sample of 43 studies was extracted by simple randomization technique, activating for 43 times random number generator in Excel, using formula `RANDBETWEEN(1;185)` for preclinical, and `RANDBETWEEN(1;149)` for clinical/observational studies.

The extracted preclinical studies were analyzed for internal methodological validity, checking whether basic principles of correct experimental design (replication, control and randomization) were followed. For the purpose of preclinical studies analysis, the checklist with 8 questions was prepared (Table 1). The extracted clinical/observational studies were analyzed for common errors in design and statistics, as earlier described in the literature (measuring bias, lack of randomization, ignoring assumptions for statistical tests, ignoring intention-to-treat analysis, etc.) (9). For the purpose of clinical/observational studies analysis, the checklist with 9 questions was prepared (Table 2). The details of the analysis of preclinical and clinical studies are shown in the Tables 3 and 4, respectively. The results are tabulated and described by rates and percentages when categorical, and by means, standard deviations, medians and interquartile ranges, if continuous. Normality of the data distribution was checked by Kolmogorov-Smirnov test, and if not achieved, Spearman's nonparametric correlation was used. Maximum acceptable probability of null hypothesis was set at 0.05. All calculations were performed by SPSS statistical program, version 18.

4. RESULTS

In total 43 journal articles describing preclinical studies were retrieved randomly from pool of 185 articles in the PubMed database defined by the inclusion and exclusion criteria, and then analyzed according to predefined criteria of research design quality. Average impact factor of the journals with preclinical studies (for the years when the articles were published) was 1.17 ± 0.42 , median impact factor was 1.46, and interquartile range 0.70. Forty-four journal articles describing clinical and observational studies were retrieved randomly from pool of 149 articles in the PubMed database defined by the inclusion and exclusion criteria, and then analyzed whether having the most frequent errors described in literature. Average impact factor of the journals with clinical/observational studies (for the years when the articles were published) was 0.94 ± 0.48 , median impact factor was 0.93, and interquartile range 0.99. Compliance of the articles with the criteria, average number of citations per article and average time elapsed from the publication of the articles are shown in the Tables 1 and 2. Only three of the an-

alyzed preclinical studies (7.0%) had all basic principles of experimental design completely implemented, and only one (2%) of the clinical/observational studies had none of the errors searched for. Details of analysis of the studies are shown in the Tables 3 and 4. Number of satisfied criteria per study was not correlated either with journal impact factor (Spearman's rho = 0.281, p = 0.068) or with number of citations (Spearman's rho = -0.079, p = 0.612). The time elapsed from the publication also was not correlated with the number of satisfied criteria per study (Spearman's rho = 0.021, p = 0.894). Number of satisfied criteria per study was not correlated either with journal impact factor (Spearman's rho = -0.168, p = 0.276) or with time elapsed from the publication (Spearman's rho = -0.294, p = 0.053). The number of citations was correlated reversely with the number of satisfied criteria per study (Spearman's rho = -0.318, p = 0.036).

5. DISCUSSION

In Bosnia and Herzegovina there are 9 indexed biomedical journals in the year 2019 deposited in Citation databases. In Web of Sciences is indexed only Bosnian Journal of Basic Medical Sciences (BJBMS) with IF-1,45. In database Scopus is indexed 7 biomedical journals: Medical Arhives (H-index is 19), BJBMS (H-index is 18), Acta Informatica Medica (H-index is 14), Acta Medica Academica (H-index is 10), Medicinski Glasnik (H-index is 10), HealthMed (H-index is 9), Acta Medica Saliniana (H-index is 3) and Folia Medica Facultatis Medicine Universitatis Saraeviensis (H-index is 1).

In Pubmed database are indexed 6 journals: Medical Archives, Matera Socio-Medica, Acta Informatica Medica, BJBMS, Medicinski Glasnik and Acta Medica Academica (14). Authors of this article wanted to make quality assessment of the statistical analysis of the data from results of investigations presented in published papers, randomly taken from deposited issues on Pubmed (abstracts) and Pubmed Central (full texts) from active six biomedical journals in Bosnia and Herzegovina regarding used methodological issues during its analysis and interpretation to be presented in scientific journals.

Requirement	Satisfied n (%)	Not satisfied n (%)	Unclear n (%)	Not applicable n (%)
Sample size reported for the experiment?	31 (72%)	12 (28%)	-	-
Number of observations reported for the experiment?	33 (77%)	10 (23%)	-	-
Value of test statistics, exact p value and degrees of freedom reported?	5 (12%)	37 (86%)	-	1 (2%)
Error bars correspond to the analysis (i.e. standard error is based on number of independent observations)?	15 (35%)	5 (12%)	2 (5%)	21 (48%)
Only independent observations were taken into account for statistical tests?	31 (72%)	6 (14%)	6 (14%)	-
Is there negative control?	33 (77%)	4 (9%)	-	6 (14%)
Was positive control necessary, and if so, was it used?	29 (65%)	9 (21%)	-	6 (14%)
Were treatments randomly allocated to experimental units?	17 (40%)	21 (49%)	-	5 (11%)
Number of citations: mean, standard deviation, median, interquartile range	1.9 ± 2.1; 1.0; 3.0			
Time passed from the publication (years): mean, standard deviation, median, interquartile range	4.7 ± 3.0; 4.0; 5.0			
Number of satisfied criteria per study: mean, standard deviation, median, interquartile range	4.3 ± 1.8; 5.0; 2.0			

Table 1. Results of the survey of the preclinical studies (n = 43).

Requirement	No n (%)	Yes n (%)	Unclear n (%)	Not applicable n (%)
Failure to specify the inclusion and exclusion criteria?	37 (84%)	7 (16%)	-	-
Failure to determine and report the error of your measurement methods?	4 (9%)	18 (41%)	-	22 (50%)
Failure to specify the exact statistical assumptions made in the analysis?	18 (41%)	26 (59%)	-	-
Failure to perform sample size analysis before the study begins?	5 (11%)	39 (89%)	-	-
Failure to implement adequate bias control measures?	11 (25%)	26 (59%)	-	7 (16%)
Failure to vigorously recruit and retain subjects?	38 (85%)	4 (10%)	-	2 (5%)
Failure to examine for normality of the data?	17 (38%)	23 (52%)	-	4 (10%)
Failure to report missing data, dropped subjects and use of an intention to treat analysis?	10 (23%)	32 (73%)	-	2 (5%)
Failure to point out the weaknesses of your own study?	17 (39%)	27 (61%)	-	-
Number of citations: mean, standard deviation, median, interquartile range	1.8 ± 1.9; 1.0; 2.8			
Time passed from the publication (years): mean, standard deviation, median, interquartile range	4.7 ± 3.2; 4.0; 3.8			
Number of satisfied criteria per study: mean, standard deviation, median, interquartile range	3.6 ± 1.8; 3.0; 3.0			

Table 2. Results of the survey of the clinical studies (n = 44).

Our study showed that minority of preclinical studies had basic principles of design completely followed (7%), and that just one of the analyzed clinical/observational studies (2%) was free from the most common

errors in design. Average impact factor of the surveyed studies was about one (what is usual for medical journals in the region), and publication date relatively recent, which means that our findings are actual. Considering preclinical studies, our findings on articles published in journals from Bosnia and Herzegovina do not differ significantly from findings of our previous study on articles published in highly cited international medical journals with high impact factor (some of the parameters were even better), and from findings of other studies, suggesting global character of this phenomenon (10). Necessity of randomization and replication of experiments on independent units of observation is not understood by many researchers, who although employing expensive technology and sophisticated measuring methods but missing randomization and/or replication do not get reliable results (11). Biological variability between independent experimental units is high, and if the treatments are not randomly assigned, or the experiments are not repeated for sufficient number of times on independent units, individual characteristics on one or a handful of experimental units will be erroneously understood as representative for the whole population, or the other way around, true characteristics of the population will remain unknown (12-15).

Results of our analysis of clinical and observational studies were even worse, and absolute number of satisfied criteria (i.e. absence of errors) was lower than that of preclinical studies. Main errors made in the clinical and observational studies were ignoring measurement errors, investigator's bias, not calculating necessary sample size and ignoring assumptions for statistical tests, especially normality of data distribution. In majority of studies the authors did not think of reliability of their measurement instruments and ignored possible measurement errors: even simple measurement of blood pressure could give misleading and incorrect results if not conducted properly and if the instrument for measuring blood pressure was not calibrated recently. Investigator's bias was also rarely thought of, and besides randomization in clinical trials, no other measures were taken to control such bias. Key question in observational clinical studies is who is collecting the data, and how certain incomplete or corrupted data are interpreted; this process should be made objective as much as possible, at least by employing two or more investigators to work together on the same data source, or to implement strict control by chief investigator over work of co-investigators. Use of statistical tests can also be misleading if their assumptions are ignored. The most frequent error of this kind is use of parametric statistical tests on data that are not distributed normally; in such situation more sensitive parametric tests will make type 1 statistical error, finding a difference where it does not exist.

The articles we analyzed in this study were cited regardless of their methodological errors and possibly biased results, and this may mislead future researchers (16, 17). It is interesting that number of citations was not

positively correlated with number of satisfied methodological criteria, suggesting that readers of the articles did not critically analyze methodological issues. Knowledge and skills of critically evaluating validity of published articles are essential for researchers, and should be given special emphasis in undergraduate and postgraduate programs in medicine (105-107).

Limitations of the study

The results of our study are limited to only one database (PubMed), and we missed to analyze other medical journals from Bosnia and Herzegovina with other kinds of editorial practices. Therefore, our results could underestimate or overestimate the problem of errors in study design, and should be interpreted with caution. The other limitation was that many published papers did not present sufficient data to allow for complete estimate of design issues.

6. CONCLUSIONS

Prevalence of preclinical and clinical/observational studies published in medical journals of Bosnia and Herzegovina that did not follow completely main principles of research design is high, but not higher than in influential international journals. Since incorrect results of published studies may adversely influence future research, it is necessary to make additional efforts through education and editorial practice to improve methodological quality of published studies. Earlier undergraduate and postgraduate statistical courses (both generic and specific) were mostly obsolete and incomplete, and the Bologna concept of teaching statistics also does not cover all essential methodological principles of both preclinical and clinical research.

Our previous study on a sample of preclinical studies published in journals with high impact factor and cited in WoS databases had already revealed this phenomenon, yet our intention in this study was to investigate with the same approach whether there are significant differences in methodological quality of articles published in less influential medical journals but indexed in the most comprehensive database of biomedical journals – PubMed. Our study showed that there are no significant differences between journals with high and relatively low impact factors in regard to the methodological quality, and this finding should be discussed further in the academic and scientific community.

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REFERENCES

1. Auger JP, Chuzeville S, Roy D, Mathieu-Denoncourt A, Xu J, Grenier D, et al. The bias of experimental design, including strain background, in the determination of critical *Streptococcus suis* serotype 2 virulence factors. *PLoS One*. 2017; 12(7): e0181920.
2. Moorhead JE, Rao PV, Anusavice KJ. Guidelines for experimental studies. *Dent Mater Off Publ Acad Dent Mater*. 1994 Jan; 10(1): 45-51.

3. Morsink MC, Dukers DF. Teaching neurophysiology, neuro-pharmacology, and experimental design using animal models of psychiatric and neurological disorders. *Adv Physiol Educ.* 2009; 33(1): 46-52.
4. Vesterinen HM, Vesterinen HV, Egan K, Deister A, Schlattmann P, Macleod MR, et al. Systematic survey of the design, statistical analysis, and reporting of studies published in the 2008 vol. of the *Journal of Cerebral Blood Flow and Metabolism*. *J Cereb Blood Flow Metab Off J Int Soc Cereb Blood Flow Metab.* 2011 Apr; 31(4): 1064-1072.
5. Fry DJ. Teaching experimental design. *ILAR J.* 2014; 55(3): 457-471.
6. Knapp TR. Why Is the One-Group Pretest-Posttest Design Still Used? *Clin Nurs Res.* 2016 Oct; 25(5): 467-472.
7. Jankovic SM, Kapo B, Sukalo A, Masic I. Evaluation of Published Preclinical Experimental Studies in Medicine: Methodology Issues. *Med Arch.* 2019 Oct; 73(5): 298-302. doi: 10.5455/medarh.2019.73.298-302.
8. Janković S. *Dizajn istraživanja*. 1st ed. Kragujevac, Serbia. Medrat, 2016.
9. Clark GT, Mulligan R. Fifteen common mistakes encountered in clinical research. *J Prosthodont Res.* 2011 Jan; 55(1): 1-6.
10. Killkenny C, Parsons N, Kadyszewski E, Festing MFW, Cuthill IC, Fry D, et al. Survey of the quality of experimental design, statistical analysis and reporting of research using animals. *PLoS One.* 2009 Nov 30; 4(11): e7824.
11. Hoerauf JM, Moss AF, Fernandez-Bustamante A, Bartels K. Study Design Rigor in Animal-Experimental Research Published in Anesthesia Journals. *Anesth Analg.* 2018; 126(1): 217-222.
12. Lazic SE. The problem of pseudoreplication in neuroscientific studies: is it affecting your analysis? *BMC Neurosci.* 2010 Jan 14; 11: 5.
13. Masic I. Medical Publication and Scientometrics. *Journal of Research in Medical Sciences.* 2013 Jun; 18(6): 624-630.
14. Masic I, Jakovljevic M, Sinanovic O, Gajovic S, Spiroski M, Jusufovic R, et al. The Second Mediterranean Seminar on Science Writing, Editing and Publishing (SWEP - 2018), Sarajevo, December 8th, 2018. *Acta Inform Med.* 2018 Dec; 26(4): 284-299. doi: 10.5455/aim.2018.26.284-299.
15. Masic I, Jankovic SM, Begic E. PhD Students and the Most Frequent Mistakes During Data Interpretation by Statistical Analysis Software. *Stud Health Technol Inform.* 2019 Jul 4; 262: 105-109.
16. Flannelly KJ, Flannelly LT, Jankowski KRB. Threats to the Internal Validity of Experimental and Quasi-Experimental Research in Healthcare. *J Health Care Chaplain.* 2018 Sep; 24(3): 107-130.
17. Campbell DT. Factors relevant to the validity of experiments in social settings. *Psychol Bull.* 1957 Jul; 54(4): 297-312.
18. Tasci I, Demir CF, Kuloglu T. Effects of Alpha Lipoic Acid on Loss of Myelin Sheath of Sciatic Nerve in Experimentally Induced Diabetic Rats. *Med Arch Sarajevo Bosnia Herzeg.* 2018 Jun; 72(3): 178-81.
19. Sankeshwari R, Ankola A, Bhat K, Bolmal U, Rao M. Evaluation of Physical Parameters of Novel Licorice Varnish Versus Fluoride and Combination Varnish: An In-Vitro Study. *Acta Medica Acad.* 2018 Nov; 47(2): 176-185.
20. Demirovic K, Slaj M, Spalj S, Slaj M, Kobaslija S. Comparison of Shear Bond Strength of Orthodontic Brackets Using Direct and Indirect Bonding Methods in Vitro and in Vivo. *Acta Inform Med.* 2018 Jun; 26(2): 125-129. doi: 10.5455/aim.2018.26.125-129.
21. Tkachenko A, Marakushyn D, Kalashnyk I, Korniyenko Y, Onishchenko A, Gorbach T, et al. A study of enterocyte membranes during activation of apoptotic processes in chronic carrageenan-induced gastroenterocolitis. *Med Glas (Zenica).* 2018 Aug 1; 15(2): 87-92.
22. Teng Y, Wang Z, Li W, Yu J, Shan Z, Liang C, et al. Mitoxantrone suppresses vascular smooth muscle cell (VSMC) proliferation and balloon injury-induced neointima formation: An in vitro and in vivo study. *Bosn J Basic Med Sci.* 2017 Nov 20; 17(4): 339-348.
23. Kouame K, Peter AI, Akang EN, Moodley R, Naidu EC, Azu OO. Histological and biochemical effects of Cinnamomum cassia nanoparticles in kidneys of diabetic Sprague-Dawley rats. *Bosn J Basic Med Sci.* 2019 May 20; 19(2): 138-145.
24. Grubor P, Mitković M, Mitković M, Grubor M. Comparison of biomechanical stability of osteosynthesis materials in long bone fractures. *Med Glas. (Zenica).* 2019 Feb 1; 16(1): 88-92.
25. Konjhodzic-Prcic A, Jakupovic S, Hasic-Brankovic L, Vukovic A. In vitro comparison of cytotoxicity of four root canal sealers on human gingival fibroblasts. *Med Arch.* 2015 Feb; 69(1): 24-27. doi: 10.5455/medarh.2015.69.24-27.
26. Ghobadian Z, Ahmadi MRH, Rezazadeh L, Hosseini E, Kokhazadeh T, Ghavam S. In Vitro Evaluation of Achillea Millefolium on the Production and Stimulation of Human Skin Fibroblast Cells (HFS-PI-16). *Med Arch.* 2015 Aug; 69(4): 212-217. doi: 10.5455/medarh.2015.69.212-217.
27. Avdić M, Džuzić N, Hasanić O, Spahić A, Smajlović Skenderagić L, Badnjević A, et al. Development of a novel biofilm classification tool and comparative analysis of result interpretation methodologies for the evaluation of biofilm forming capacity of bacteria using tissue culture plate method. *Med Glas. (zenica).* 2019 Feb 1; 16(1): 13-21.
28. Karcic E, Aljicevic M, Bektas S, Karcic B. Antimicrobial Susceptibility/Resistance of Streptococcus Pneumoniae. *Mater Sociomed.* 2015 Jun; 27(3): 180-184. doi: 10.5455/msm.2015.27.180-184.
29. Pinar N, Akillioglu K, Sefil F, Alp H, Sagir M, Acet A. Effect of clozapine on locomotor activity and anxiety-related behavior in the neonatal mice administered MK-801. *Bosn J Basic Med Sci.* 2015 Aug 11; 15(3): 74-79.
30. Ozyigit F, Kucuk A, Akcer S, Tosun M, Kocak FE, Kocak C, et al. Different dose-dependent effects of ebselen in sciatic nerve ischemia-reperfusion injury in rats. *Bosn J Basic Med Sci.* 2015 Aug 26; 15(4): 36-43.
31. Durić K, Kovac Besovic EE, Niksic H, Muratovic S, Sofic E. Anti-coagulant activity of some Artemisia dracuncululus leaf extracts. *Bosn J Basic Med Sci.* 2015 May 13; 15(2): 9-14.
32. Rachman A, Rantam FA, Bachtiar I, Fatchiyah F, Hakim L, Putri IL, et al. Biocompatibility of Ytria-Tetragonal Zirconia Polycrystal Seeded with Human Adipose Derived Mesenchymal Stem Cell. *Acta Inform Med.* 2018 Dec; 26(4): 249-253. doi: 10.5455/aim.2018.26.249-253.
33. Iamsaard S, Sukhorum W, Samrid R, Yimdee J, Kanla P, Chaisiwamongkol K, et al. The sensitivity of male rat reproductive organs to monosodium glutamate. *Acta Medica Acad.* 2014; 43(1): 3-9.
34. Topaloglu-Ak A, Onçağ O, Gökçe B, Bent B. The effect of different enamel surface treatments on microleakage of fissure sealants. *Acta Medica Acad.* 2013 Nov; 42(2): 223-228.
35. Guo L, Tan K, Luo Q, Bai X. Dihydromyricetin promotes autophagy and attenuates renal interstitial fibrosis by regulating miR-

- 155–5p/PTEN signaling in diabetic nephropathy. *Bosn J Basic Med Sci.* 2019 Oct 31;
36. Kapić D, Mornjaković Z, Čosović E, Šahinović M. A histological study of the effect of exogenous melatonin on gentamicin induced structural alterations of proximal tubules in rats. *Bosn J Basic Med Sci.* 2014 Feb; 14(1): 30–34.
 37. Cervera-Irimia J, González-Miranda Á, Riquelme-García Ó, Burgos-Flores J, Barrios-Pitarque C, García-Barreno P, et al. Scoliosis induced by costotransversectomy in minipigs model. *Med Glas (Zenica).* 2019 Aug 1; 16(2).
 38. Minbay Z, Serter Kocoglu S, Gok Yurtseven D, Eyigor O. Immunohistochemical localization of ionotropic glutamate receptors in the rat red nucleus. *Bosn J Basic Med Sci.* 2017 Feb 21; 17(1): 29–37.
 39. Solmaz A, Gülçiçek OB, Erçetin C, Yiğitbaş H, Yavuz E, Arıcı S, et al. Nesfatin-1 alleviates extrahepatic cholestatic damage of liver in rats. *Bosn J Basic Med Sci.* 2016 Nov 10; 16(4): 247–253.
 40. Chen J, Zheng G, Guo H, Shi Z-N, Jiang J, Wang X-Y, et al. The effect of metformin treatment on endoplasmic reticulum (ER) stress induced by status epilepticus (SE) via the PERK-eIF2 α -CHOP pathway. *Bosn J Basic Med Sci.* 2018 Feb 20; 18(1): 49–54.
 41. Nefic H, Musanovic J, Metovic A, Kurteshi K. Chromosomal and nuclear alterations in root tip cells of allium cepa L. Induced by alprazolam. *Med Arch.* 2013 Dec; 67(6): 388–392. doi: 10.5455/medarh.2013.67.388–392.
 42. Jiang S, Hu L, Ping L, Sun F, Wang X. Glutathione protects against hepatic injury in a murine model of primary Sjögren's syndrome. *Bosn J Basic Med Sci.* 2016 Aug 2; 16(3): 227–231.
 43. Murai Y, Ohta T, Tadaki H, Miyajima K, Shinohara M, Fatchiyah F, et al. Assessment of Pharmacological Responses to an Anti-diabetic Drug in a New Obese Type 2 Diabetic Rat Model. *Med Arch.* 2017 Dec; 71(6): 380–384. doi: 10.5455/medarh.2017.71.380–384.
 44. Al-Qahdi SS, Alzohari N, Alsaid AY, Ashour AA, Aboukassim T, Vranic S, et al. Teucrium Polium Plant Extract Provokes Substantial Cytotoxicity at the Early Stage of Embryonic Development. *Bosn J Basic Med Sci.* 2019 Feb 12; 19(1): 67–71.
 45. Islami H, Bexheti S, Ahmetaj H, Sukalo A, Manxhuka S, Nuraj B, et al. Action of propranolol in the reaction of smooth musculature of tracheal rings induced with acetylcholine, histamine, serotonin (5-HT) and prostaglandin (PGF $_2$ -alfa) in vitro and in vivo. *Bosn J Basic Med Sci.* 2009 May; 9(2): 142–147.
 46. Wang S, Zhou J, Kang W, Dong Z, Wang H. Tocilizumab inhibits neuronal cell apoptosis and activates STAT3 in cerebral infarction rat model. *Bosn J Basic Med Sci.* 2016 Jan 15; 16(2): 145–150.
 47. Rizvić E, Janković G, Kostić-Rajačić S, Savić MM. Atypical sympathomimetic drug lerimazoline mediates contractile effects in rat aorta predominantly by 5-HT $_2A$ receptors. *Bosn J Basic Med Sci.* 2017 Aug 20; 17(3): 194–202.
 48. Milutinović A. Lithium chloride could aggravate brain injury caused by 3-nitropropionic acid. *Bosn J Basic Med Sci.* 2016 Nov 10; 16(4): 261–267.
 49. Medenica-Milanović S, Ristić S, Turuntas V, Mirić M, Kulić M. Registration and analysis of bioelectric activity of sensory-motor cortex during the electrical stimulation of nucleus caudate in rats. *Bosn J Basic Med Sci.* 2007 May; 7(2): 155–161.
 50. Wang X, Wang C, Yang Y, Ni J. New monocyte locomotion inhibitory factor analogs protect against cerebral ischemia-reperfusion injury in rats. *Bosn J Basic Med Sci.* 2017 Aug 20; 17(3): 221–227.
 51. Durendić-Brenesel M, Popović T, Pilija V, Arsić A, Milić M, Kojić D, et al. Hypolipidemic and antioxidant effects of buckwheat leaf and flower mixture in hyperlipidemic rats. *Bosn J Basic Med Sci.* 2013 May; 13(2): 100–108.
 52. Tas T, Kocoglu E, Mengeloglu Z, Bucak O, Karabörk S. Investigation of in-vitro susceptibility of multidrug-resistant *Acinetobacter baumannii* strains isolated from clinical specimens to tigecycline. *Bosn J Basic Med Sci.* 2013 Nov; 13(4): 266–270.
 53. Kir HM, Sahin D, Oztaş B, Musul M, Kuskay S. Effects of single-dose neuropeptide Y on levels of hippocampal BDNF, MDA, GSH, and NO in a rat model of pentylentetrazole-induced epileptic seizure. *Bosn J Basic Med Sci.* 2013 Nov; 13(4): 242–247.
 54. Ge Y, Zhang J, Cao J, Wu Q, Sun L, Guo L, et al. TFF1 inhibits proliferation and induces apoptosis of gastric cancer cells in vitro. *Bosn J Basic Med Sci.* 2012 May; 12(2): 74–81.
 55. Ozdemir E, Bagcivan I, Gursoy S. Role of D $_1$ /D $_2$ dopamin receptors antagonist perphenazine in morphine analgesia and tolerance in rats. *Bosn J Basic Med Sci.* 2013 May; 13(2): 119–125.
 56. Li T, Mao J, Huang L, Fu H, Chen S, Liu A, et al. Huaqihuang may protect from proteinuria by resisting MPC5 podocyte damage via targeting p-ERK/CHOP pathway. *Bosn J Basic Med Sci.* 2016 Aug 2; 16(3): 193–200.
 57. Keskin N, Mammadov R, Ili P. The effects of *Crataegus aronia* var. *dentata* Browicz extract on biochemical indices and apoptosis in partially hepatectomized liver in rats. *Bosn J Basic Med Sci.* 2012 Aug; 12(3): 177–181.
 58. Özkan F, Çakır-Özkan N, Eyibilen A, Yener T, Erkorkmaz Ü. Comparison of ketamine-diazepam with ketamine-xylazine anesthetic combinations in sheep spontaneously breathing and undergoing maxillofacial surgery. *Bosn J Basic Med Sci.* 2010 Nov; 10(4): 297–302.
 59. Cekic V, Vasovic V, Jakovljevic V, Mikov M, Sabo A. Hypoglycaemic action of stevioside and a barley and brewer's yeast based preparation in the experimental model on mice. *Bosn J Basic Med Sci.* 2011 Feb; 11(1): 11–16.
 60. Beriat GK, Akmansu SH, Ezerarslan H, Dogan C, Han U, Saglam M, et al. The comparison of thermal tissue injuries caused by ultrasonic scalpel and electrocautery use in rabbit tongue tissue. *Bosn J Basic Med Sci.* 2012 Aug; 12(3): 151–157.
 61. Omerbegovic M. Linear Short-Term Heart Rate Variability Parameters of Subjects Tobacco Cigarette Smokers and Subjects Nonsmokers in Preoperative Period. *Med Arch.* 2017 Feb; 71(1): 12–15. doi: 10.5455/medarh.2017.71.12–15.
 62. Nouraei SM, Baradari AG, Jazayeri A. Does Remote Ischaemic Preconditioning Protect Kidney and Cardiomyocytes After Coronary Revascularization? A Double Blind Controlled Clinical Trial. *Med Arch.* 2016 Oct; 70(5): 373–378. doi: 10.5455/medarh.2016.70.373–378.
 63. Kefeli A, Basyigit S, Yeniova AO, Kefeli TT, Aslan M, Tanas O. Comparison of three different regimens against *Helicobacter pylori* as a first-line treatment: A randomized clinical trial. *Bosn J Basic Med Sci.* 2016 Jan 1; 16(1): 52–57.
 64. Softić I, Tahirović H, Di Ciommo V, Auriti C. Bacterial sepsis in neonates: Single centre study in a Neonatal intensive care unit in Bosnia and Herzegovina. *Acta Medica Acad.* 2017 May; 46(1): 7–15.
 65. Đug H, Jagodić S, Ahmetović-Đug J, Selimović Z, Sulejmanović A. Predicting recurrence of non-muscle-invasive bladder cancer after transurethral resection. *Med Glas. (Zenica).* 2016 Feb 1; 13(1): 56–61.

66. Velija-Asimi Z, Burekovic A, Dujic T, Dizdarevic-Bostandzic A, Semiz S. Incidence of prediabetes and risk of developing cardiovascular disease in women with polycystic ovary syndrome. *Bosn J Basic Med Sci.* 2016 Nov 10; 16(4): 298-306.
67. Solaković E, Totić D, Solaković S. Femoro-popliteal bypass above knee with saphenous vein vs synthetic graft. *Bosn J Basic Med Sci.* 2008 Nov; 8(4): 367-372.
68. Cerović A, Miletić I, Konić-Ristić A, Baralić I, Djordjević B, Djurčić I, et al. The dry plant extract of common bean seed (*Phaseoli vulgaris pericarpium*) does not have an effect on post-prandial glycemia in healthy human subject. *Bosn J Basic Med Sci.* 2006 Aug; 6(3): 28-33.
69. Soell M, Feki A, Hannig M, Sano H, Pinget M, Selimovic D. Chromogranin A detection in saliva of type 2 diabetes patients. *Bosn J Basic Med Sci.* 2010 Feb; 10(1): 2-8.
70. Heljić B, Velija-Asimi Z, Kulić M. The statins in prevention of coronary heart diseases in type 2 diabetics. *Bosn J Basic Med Sci.* 2009 Feb; 9(1): 71-76.
71. Džubur Kulenović A, Memić Serdarević A, Halilović Z, Mašnić H, Bahto A, Kapo B, et al. Observational multicenter study of efficacy of paroxetine filmcoated tablet in the treatment of anxiety disorder. *Med Glas. (Zenica).* 2018 Aug 1; 15(2): 186-191.
72. Emren SV, Zoghi M, Berilgen R, Özdemir İH, Çelik O, Çetin N, et al. Safety of once- or twice-daily dosing of non-vitamin K antagonist oral anticoagulants (NOACs) in patients with nonvalvular atrial fibrillation: A NOAC-TR study. *Bosn J Basic Med Sci.* 2018 May 20; 18(2): 185-190.
73. Asheghan M, Aghda AK, Hashemi E, Hollisaz M. Investigation of the effectiveness of acupuncture in the treatment of frozen shoulder. *Mater Sociomed.* 2016 Jul 24; 28(4): 253-257. doi: 10.5455/msm.2016.24.253-257.
74. Huang W-N, Tso TK. Etoricoxib improves osteoarthritis pain relief, joint function, and quality of life in the extreme elderly. *Bosn J Basic Med Sci.* 2018 Feb 20; 18(1): 87-94.
75. Sandesc M, Rogobete AF, Bedreag OH, Dinu A, Papurica M, Cradigati CA, et al. Analysis of oxidative stress-related markers in critically ill polytrauma patients: An observational prospective single-center study. *Bosn J Basic Med Sci.* 2018 May 20; 18(2): 191-197.
76. Maleškić S, Kusturica J, Gušić E, Rakanović-Todić M, Šečić D, Burnazović-Ristić L, et al. Metformin use associated with protective effects for ocular complications in patients with type 2 diabetes - observational study. *Acta Medica Acad.* 2017 Nov; 46(2): 116-123.
77. Jahić D, Omerović D, Tanović AT, Dzanković F, Campara MT. The Effect of Prehabilitation on Postoperative Outcome in Patients Following Primary Total Knee Arthroplasty. *Med Arch.* 2018 Dec; 72(6): 439-443.
78. Nurkić J, Al-Ahmad M, Maher A, Arifhodžić N, Jusufović E. Most common, real life factors affecting effectiveness of omalizumab asthma treatment: 10-year study. *Med Glas (Zenica).* 2019 Feb 1; 16(1): 45-52.
79. Smajić J, Hasić S, Rašić S. High-density lipoprotein cholesterol, apolipoprotein E and atherogenic index of plasma are associated with risk of chronic kidney disease. *Med Glas (Zenica).* 2018 Aug 1; 15(2): 115-121.
80. Sukalo A, Deljo D, Krupalija A, Zjajo N, Kos S, Curic A, et al. Treatment of Hypertension with Combination of Lisinopril/Hydrochlorothiazide. *Med Arch.* 2016 Jul 27; 70(4): 299-302. doi: 10.5455/medarh.2016.27.299-302.
81. Alibašić E, Skopljak A, Čengić A, Krstović G, Trifunović N, Čatić T, et al. Efficacy of carbocisteine in the treatment of chronic obstructive pulmonary disease and impact on the quality of life. *Med Glas (Zenica).* 2017 Aug 1; 14(2): 182-188.
82. Sinković A, Masnik K, Mihevc M. Predictors of acute kidney injury (AKI) in high-risk ST-elevation myocardial infarction (STEMI) patients: A single-center retrospective observational study. *Bosn J Basic Med Sci.* 2019 Feb 12; 19(1): 101-108.
83. Begovic B, Ahmetagic S, Calkic L, Vehabovic M, Kovacevic SB, Catic T, et al. Open Clinical Trial on Using Nifuroxazide Compared to Probiotics in Treating Acute Diarrhoeas in Adults. *Mater Sociomed.* 2016 Dec; 28(6): 454-458. doi: 10.5455/msm.2016.28.454-458.
84. Stanetić K, Petrović V, Marković B, Stanetić B. The Presence of Stress, Burnout Syndrome and the Most Important Causes of Working Stress Among Physicians in Primary Health Care - an Observational Study from Banja Luka, Bosnia and Herzegovina. *Acta Medica Acad.* 2019 Aug; 48(2): 159-166.
85. Perić S, Bubanj M, Bubanj S, Jančić S. Side effects assessment in glycolic acid peelings in patients with acne type I. *Bosn J Basic Med Sci.* 2011 Feb; 11(1): 52-57.
86. Alimian M, Mohseni M, Safaeian R, Faiz SHR, Majedi MA. Comparison of hydroxyethyl starch 6% and crystalloids for preloading in elective caesarean section under spinal anesthesia. *Med Arch.* 2014 Aug; 68(4): 279-281. doi: 10.5455/medarh.2014.68.279-281.
87. Tanovic E. Effects of functional electrical stimulation in rehabilitation with hemiparesis patients. *Bosn J Basic Med Sci.* 2009 Feb; 9(1): 49-53.
88. Loncar D, Varjagic M, Novakovic T, Milovanovic D, Jankovic S. Correlation between serum biochemical markers and early amniocentesis in diagnosis of congenital fetal anomalies. *Bosn J Basic Med Sci.* 2010 Feb; 10(1): 9-14.
89. Breazu CM, Ciobanu L, Bartos A, Bodea R, Mircea PA, Ionescu D. Pethidine efficacy in achieving the ultrasound-guided oblique subcostal transversus abdominis plane block in laparoscopic cholecystectomy: A prospective study. *Bosn J Basic Med Sci.* 2017 Feb 21; 17(1): 67-73.
90. Xu X, Ma H, Xu J, Huang H, Wu X, Xiong Y, et al. Elevation in circulating YKL-40 concentration in patients with cerebrovascular disease. *Bosn J Basic Med Sci.* 2014 Aug 14; 14(3): 120-124.
91. Alkhalidi HM, Salaita WM, Shabaneh MA, Al-Horut MI, Aldabbas RMAA, Uraiqat AA. Postoperative Outcome Comparison Between Pudendal Nerve Block and Caudal Block After Lateral Open Internal Sphincterotomy. *Med Arch.* 2015 Jun; 69(3): 187-189. doi: 10.5455/medarh.2015.69.187-189.
92. Ledari FM, Barat S, Delavar MA. Chewing gums has stimulatory effects on bowel function in patients undergoing cesarean section: a randomized controlled trial. *Bosn J Basic Med Sci.* 2012 Nov; 12(4): 265-268.
93. Kunt A, Özcan S, Küçükler A, Odabaşı D, Sami Kunt A. Effects of perioperative statin treatment on postoperative atrial fibrillation and cardiac mortality in patients undergoing coronary artery bypass grafting: a propensity score analysis. *Med Glas (Zenica).* 2015 Aug; 12(2): 190-195.
94. Esparza M, Wild JR, Minnock C, Mohty KM, Truchan LM, Taljanovic MS. Ultrasound Evaluation of Radial Nerve Palsy Associated with Humeral Shaft Fractures to Guide Operative Versus Non-Operative Treatment. *Acta Medica Acad.* 2019 Aug; 48(2): 183-192.

95. Saadia Z. Urinary Problems Amongst Gynecological Consultations. Association Between Prolapse, Gynecological Surgery and Diabetes.. *Mater Sociomed.* 2016 Jun; 28(3): 183-186. doi: 10.5455/msm.2016.28.183-186.
96. Mhaskar R, B Bercu B, Djulbegovic B. At what level of collective equipoise does a randomized clinical trial become ethical for the members of institutional review board/ethical committees? *Acta Inform Med.* 2013; 21(3): 156-159. doi: 10.5455/aim.2013.21.156-159.
97. Saadia Z. Rates and Indicators for Episiotomy in Modern Obstetrics - a study from Saudi Arabia. *Mater Sociomed.* 2014 Jun; 26(3): 188-190. doi: 10.5455/msm.2014.26.188-190.
98. Nuraj P, Hyseni N. The Role of the Tamsulosin in the Medical Expulsion Therapy for Distal Ureteral Stones. *Med Arch.* 2017 Apr; 71(2): 137-140. doi: 10.5455/medarh.2017.71.137-140.
99. Hasic S, Kadic D, Kiseljakovic E, Jadric R, Spahic E. Serum Uric Acid Could Differentiate Acute Myocardial Infarction and Unstable Angina Pectoris in Hyperuricemic Acute Coronary Syndrome Patients. *Med Arch.* 2017 Apr; 71(2): 115-118. doi: 10.5455/medarh.2017.71.115-118.
100. Dehghan M. Comparative effectiveness of B and e vitamins with diclofenac in reducing pain due to osteoarthritis of the knee. *Med Arch.* 2015 Apr; 69(2): 103-106. doi: 10.5455/medarh.2015.69.103-106.
101. Maksić H, Heljić S, Skokić F, Šumanović-Glamuzina D, Milošević V, Zlatanović A, et al. Predictors and incidence of hospitalization due to respiratory syncytial virus (RSV)-associated lower respiratory tract infection (LRTI) in non-prophylaxed moderate-to-late preterm infants in Bosnia and Herzegovina. *Bosn J Basic Med Sci.* 2018 Aug 1; 18(3): 279-288.
102. Mangi AM, Bansal V, Li G, Pieper MS, Gajic O, Festic E. Pre-hospital use of inhaled corticosteroids and inhaled beta agonists and incidence of ARDS: A population-based study. *Acta Medica Acad.* 2015; 44(2): 109-116.
103. Pajaziti L, Vasili E. Treatment of Onychomycosis - a Clinical Study. *Med Arch.* 2015 Jun; 69(3): 173-176. doi: 10.5455/medarh.2015.69.173-176.
104. Fouladi A, Soleimani A. Comparison of Different Analgesic Techniques for Pain Relief During Extracorporeal Shock Wave Lithotripsy: a Double-blind, Randomized Clinical Trial. *Acta Inform Med.* 2017 Jun; 27(2): 94-98. doi: 10.5455/aim.2017.27.94-98.
105. Masic I, Kujundzic E. Science Editing in Biomedicine and Humanities. *Avicena.* 2013: 272 pages. ISBN: 978-9958-720-49-9..
106. Masic I, Begic E, Donev MD, Gajovic S, Gasparyan YA, Jakovljevic M, Milosevic D. et al. Sarajevo Declaration on Integrity and Visibility of Scholarly Journals. *Croat Med J.* 2016; 57527-529.
107. Mohammadali M. Shoja, Anastasia Arynchna (Eds.). *A Guide to the Scientific Career.* Willey Blackwell. London, 2019: 163-178

The screenshot shows the IMIA website homepage. At the top, there is a dark blue header with the IMIA logo on the left and the text 'International Medical Informatics Association' on the right. Below the header, there are navigation links: 'About Us', 'IMIA Members', 'Publications', 'MedInfo', 'IMIA WGs & SIGs', 'IMIA NI SIG', and 'IAHSI'. On the right side of the header, there is a small promotional banner for 'NI 2020' in Brisbane, Australia, from July 27-29, 2020.

The main content area is white. It starts with a 'Welcome to IMIA!' section, followed by a 'General' section containing introductory text about the organization. Below this is a 'Purpose, Goals, Objectives' section with a list of goals. The 'Membership' section follows, detailing the types of members and the process of joining. At the bottom of the main content, there is an 'Upcoming Events' section with a calendar view showing events for May, June, and July 2020.

On the right side of the page, there is a 'Login' form with fields for 'Username' and 'Password', and a 'Remember Me' checkbox. Below the login form, there is a 'Yearbook of Medical Informatics' section with a book cover image. Further down, there are several news items, including 'IMIA - Latest News', 'CAREER OPPORTUNITY - DEAN, FACULTY OF HUMAN AND SOCIAL DEVELOPMENT', 'THE 2ND CHINESE NURSING INFORMATICS CONFERENCE - CALL FOR ABSTRACTS, DEADLINE OCTOBER 20, 2019', 'MIE 2020 - PAPER SUBMISSION DEADLINE OCTOBER 15TH, 2019', 'CALL FOR SUBMISSIONS OPEN FOR NI 2020 IN BRISBANE 27-29 JULY', and 'DON LINDBERG'. At the bottom right, there is a 'VIEW CALENDAR' button.