ISSN 2709-2968
eISSN 2709-2976

VOLUME 3 ISSUE 2 2022

Journal of Interdisciplinary Approaches to Medicine

Al-Farabi Kazakh National University

Journal of Interdisciplinary Approaches to Medicine

Proprietor of the Edition: Al-Farabi Kazakh National University
Editor-in-chief: Zh.A. Kalmatayeva

Certificate № 17781-СИ Registered on July 4th, 2019 in the Ministry of Information and communications of the Republic of Kazakhstan

Computer page makeup and cover designer: *U. Moldasheva*

Format 60x84/8. Offset paper.
Digital printing. Volume printer's 5,0 sheet.
Publishing house «Kazakh University»
Al-Farabi Kazakh National University
KazNU, 71 Al-Farabi, 050040, Almaty
Printed in the printing office of the Publishing house «Kazakh University».

Section 1
Research articles

IRSTI 76.29.51: https://doi.org/10.26577/IAM.2022.v3.i2.01

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A DESCRIPTIVE STUDY OF EPILEPTIC PATIENTS IN HERAT CITY OF AFGHANISTAN

Epilepsy is one of the most common and serious neurological disorders which is characterized by recurrent unprovoked seizures. Its prevalence ranges from 0.5% to 1% of the population in developed countries, and even higher in developing countries. Around 70 million people worldwide have epilepsy.

This research aims to perform a descriptive study on epileptic children 7-18 years old in Herat city of Afghanistan.

This descriptive study was performed on 7-18 years old children with epilepsy, which was conducted from in 2021 in Herat city of Afghanistan. The study included 100 patients with epileptic disorders, in this study Encephalography, Magnetic resonance imaging, Computed tomography, and Sociodemographic information were used to describe the patients.

The main group of this study included 100 epileptic children. The age of study participants ranged from 7- 18 years and the mean age was 9.21 ± 2.64 years. 46 (51.1%) were males and 44 (48.9%) were females. More often Epilepsy cases were observed in patients with focal seizures. Hereditary predisposition was found as a risk factor and it was statistically significant, the p-value was less than 0.0007. Having status epilepsy was also found a risk factor for epilepsy and the p-value was 0.001. Also, prognostic factors for refractory epilepsy were determined in this study.

The risk factors that were found in epileptic patients, were high and comparable with other studies in the world literature. More often epilepsy cases were determined in patients with focal seizures, hereditary predisposition, and having status epilepsy also found as prevalent risk factors for refractory epilepsy. Also, prognostic factors for epilepsy were identified. Negative factors were a high number of seizures, abnormal electroencephalography findings, and early onset of seizures in epileptic patients.

Keywords: Epilepsy, Seizure, Children.

Introduction

A seizure is a paroxysmal alteration of neurologic function caused by the excessive, hypersynchronous discharge of neurons in the brain. “Epilepsy” is the condition of recurrent, unprovoked seizures. Epilepsy has numerous causes, each reflecting underlying brain dysfunction [1]. The outward effects can vary from wild thrashing movements (tonic-clonic) seizures to milder types with a brief loss of awareness Petidmal seizure [2]. Epilepsy previously has been defined as at least two unprovoked seizures >24 h apart [3].

Epilepsy is a prevalent problem in the world, around 70 million people worldwide have epilepsy, mostly among children and adolescents. (WHO, 2019) [4,5]. Epilepsy is one of the most common neurological disorders, Its prevalence ranges from 0.5% to 1% of the population in developed countries and even higher in developing countries [6].

In a study which was done in Iran, the point prevalence of active epilepsy was 7.87 per 1000 individuals [7]. And in Canada, the prevalence of epilepsy in children in a national survey was 5.26/1000 [8]. The preferred initial management approach in epilepsy treatment as antiepileptic drug monotherapy is generally accepted. Even though, up to 30% of patients with epilepsy do not respond well to conventional antiepileptic medication, either due to recurrent seizures despite optimized antiepileptic drug therapy or due to adverse effects [9]. And juvenile myoclonic epilepsy is known to be subject to an elevated risk of seizures for several decades [10]. Structural brain lesions, such as malformations of cortical development are factors in the recurrence

of seizures as well [11]. Also, Kim JH, and his colleagues found a relationship between seizures and some triggers, the age of seizure onset commonly ranges among stimuli such as insomnia, fatigue, and stress [12]. In addition, epilepsy is associated with increased risk for morbidity and mortality, and can severely decrease the quality of life of a person with epilepsy. [13]. Furthermore, mental disorders including depression and anxiety in these patients and their families are more common compared to the general population [14]. For a more detailed account of the definitions and classification of epileptiform EEG abnormalities, the reader is referred to Seneviratne et al [15]. Also, there has been a recent explosion of new information regarding the genetic basis of epilepsy syndromes. Both monogenic and polygenic mutations can lead to epilepsy [16]. Also computed tomography (CT) and magnetic resonance imaging (MRI) scans are positive adjuncts to the clinical examination and EEG in the evaluation of a patient with seizures. Neuroimaging techniques are especially sensitive for central nervous system (CNS) structural lesions [17].

Aim of the research:

The aim of this research is to perform a descriptive study on epileptic children 7-18 years old in Herat city of Afghanistan.

Materials and Methods

This study is an observational study that describes the status, not the intervention. This study design is as descriptive and analytic, in that the data was analyzed and the group and categories were compared in this study. This study was held prospectively in the neurological center in Herat-Afghanistan. This research aims to study epilepsy in epileptic children 7-18 years old in Herat city of Afghanistan. And the study has objectives which are explained in the introduction part. For the achievement of the mentioned aim and objectives, the following steps were done. Patients who meet the inclusion criteria, regardless from which district of the Herat providence were randomly selected and recruited for this study. For the participation patients or their companions should sign the informed consent for the present study.

Criteria of inclusion:

- Patients with epilepsy.
- Children aged 7-18 years
- All patients and their legally authorized representatives who have given consent for participation.

Criteria of exclusion:

- Patient didn't have epilepsy
- Patients, age older 7 years & Age younger 18 years.
- All patients who did not agree to participate.
- Patients with epilepsy who had severe mental retardation.

Categorical data were presented as a percentage, and comparisons between groups were performed using the chi-square test or Fisher's exact test. The probability of an error of the first kind (the probability of an erroneous conclusion about the existence of differences between groups) was <5%, which is considered acceptable in medical research. Moreover, for all data types, a P-value less than 0.05 was designated as statistically significant.

Data processing was carried out using the data analysis package for the spreadsheet processor «Excel 2018» Microsoft® Office, «IBM-SPSS Statistics version 26» for Windows presented as mean ± SD or median, All patients participated voluntarily and informed consent was signed by children and their caregivers.

Results

In this study, 100 epileptic patients were included, whose characteristic was studied and described here.

Patients were included at an average age of 9.21 ± 2.64 ranging from (7 to 18 years old), with 46 men and 44 women (50 % and 49 %, respectively). In this investigation, a hereditary propensity was discovered in 50 (55.5%) cases, more than other risk factors ($P < 0.05$). Patients' average age at the start of their seizures was 4.1± 3. Also in this study, the average duration of illness in children was found 5.9 ± 3.21 years.

When patients were analyzed based on the frequency of their seizures, (31%) of them were recognized to have frequent seizures, with (14.2%) was experiencing numerous seizures virtually every day.

Generalized seizures were shown to be the most common type of seizure in epilepsy patients and 51 (56.7%) had primary generalized seizures the test was significant ($P<0.003$).

During MRI, pathogenic alterations in the form of mild cortical-subcortical atrophy were found in 23 patients. 32 individuals had symptoms of ventriculomegaly, while 26 patients exhibited small local atrophy.

48 patients (53.3%) in this study underwent effective therapy. Additionally, 42 (46.7%) kids and teenagers lacked remission. Drug-resistant epilepsy affected 26 patients (28.9%).

As there is shown in (Table 2) 66.7% of epileptic children experienced refractory epilepsy during

their illness. Secondary and primary generalized seizures both were with status epilepsy, but the two other groups were not and the test was statistically significant (P-value < 0.0001).

(Table 1) shows that hereditary predisposition was the most common risk factor of epilepsy, especially in boys (71.4%). Consequently, was perinatal pathology and this difference was statistically significant (P<0.05).

The average age of epileptic children at the time of the last visit was 9.21 ± 2.64 years and (male 50 % and female 49 %), gender difference with a predominance of male patients was significant (P <0.05) as there are demonstrated by (Figure 1).

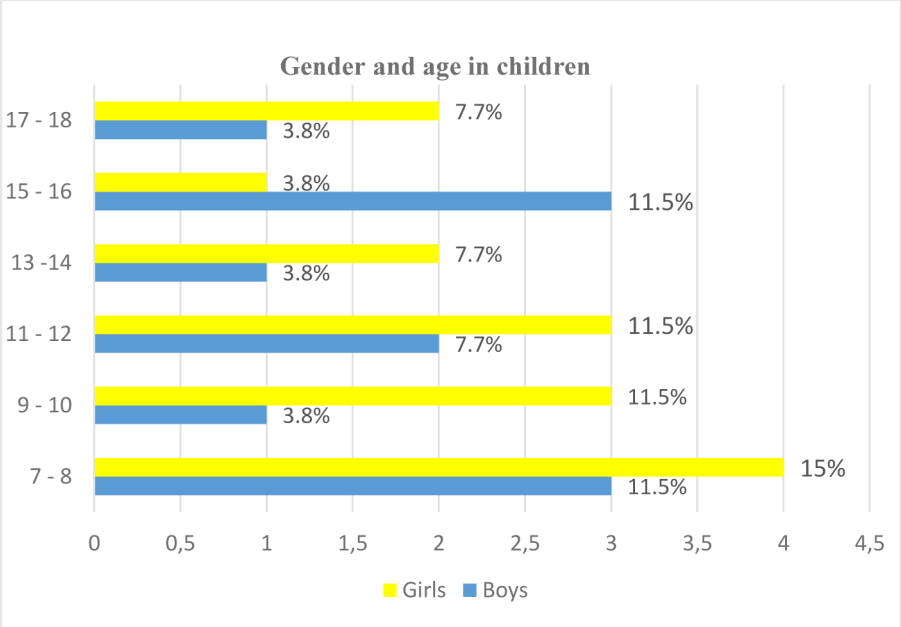

Figure 1 – Children with epilepsy by gender and age

As there is shown in (Table 1) hereditary predisposition was the most prevalent risk factor. The second step was perinatal pathology and this difference was statistically significant (P<0.05).

Table 1 – The risk factors in epileptic patients.

Risk factor	Male		Female		
	Frequency	%	Frequency	%	
Perinatal pathology, including traumatic brain injury	16	38.1	23	47.9	
Hereditary predisposition for epilepsy	30	71.4	30	62.5	
Febrile seizures	16	38.1	11	22.9	
No risk factors identified	1	2.4	0	0.0	
Early neuro-infections in children	0	0.0	0	0.0	
Pathology of pregnancy	0	0.0	0	0.0	
Somatic pathology	0	0.0	0	0.0	P<0.004

As presented in (Figure 2) severe seizures were observed in (12%) of all patients, but daily attacks were seen in (12.3%) of epileptic patients.

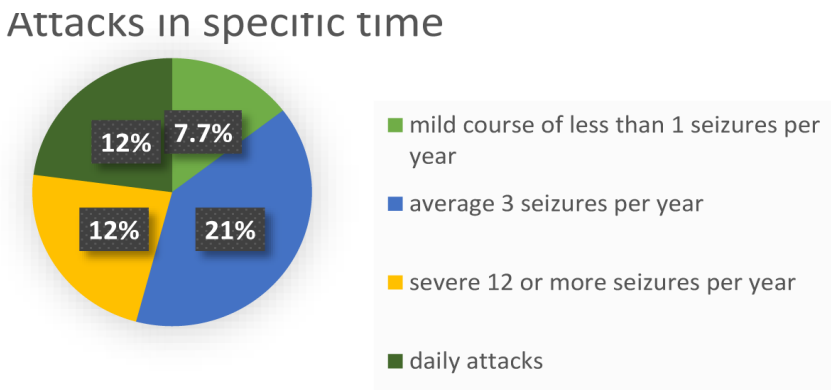

Figure 2 – Seizure's numbers in this study patients

In 23.6% of patients, simple or complex partial seizures were noted at the onset of the disease and in 28.5% of patients were marked by the appearance of secondary generalized tonic-clonic seizures. And 57% had primary generalized seizures as presented in (Figure 3). And the result of the test was found statistically significant (P<0.003).

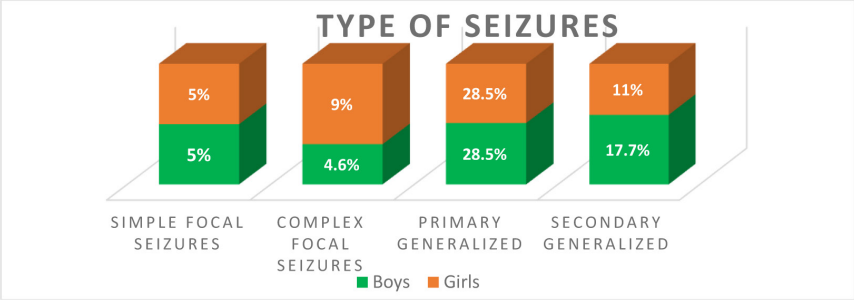

Figure 3 – Type of seizures in this study patients

Diffuse changes in the electrical activity of the brain in the interictal EEG were observed in (25.5%) of patients, but local paroxysmal activities were seen in (14%) of patients. Hippocampal theta rhythm detected in (32%) of epileptic children, as demonstrated in (Figure 4).

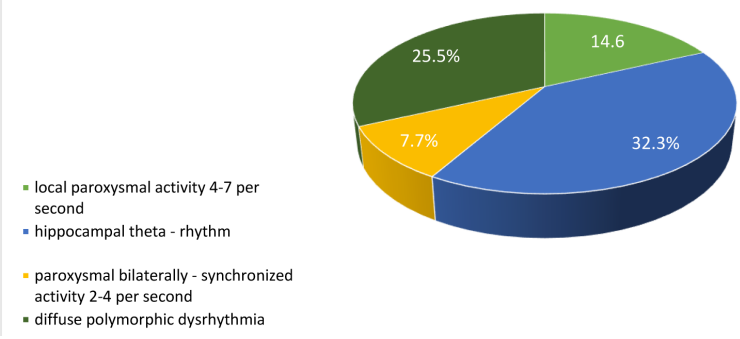

Figure 4 – Electroencephalographic findings in epileptic children.

The epileptic children who participated in this research, were studied by the difference between the type of seizures and having status epilepsy. As there is shown in (Table 2) it's statistically significant (p-value was less than 0.0001) type of seizures was different by having status epilepsy. Primary generalized seizure and secondary generalized had status epilepsy but two other categories didn't have status attacks.

Table 2 – Distribution of seizure types by having status epilepsy in patients

Type of seizure	Status Epilepsy attacks				
	Yes		No		
	Numbers	%	Numbers	%	
Complex focal seizure	0	0.0	8	25.8	P Value <0.0001
Simple focal seizure	0	0.0	8	25.8	
Primary Generalized	44	74.6	8	25.8	
Secondary Generalized	15	25.4	7	22.6	

Discussion

In this research, the characteristic of epilepsy is studied and described in epileptic patients.

The average age of patients at the time of inclusion was 9.21 ± 2.64 (from 7 to 18 years old) and 46 males (50 %) and 44 females (49 %). But in a study which was conducted by Lauren Conway and her colleagues, the gender difference found was (56.5% male and 43.5 female) [18] was near to this study's result.

Hereditary predisposition was found in 50 (55.5%) in this study. But in a study which was done by Kourosh and his colleagues in Iran, they found the proportion of hereditary predisposition in epileptic patients was 26% [19]. This proportion is almost half of our findings. And maybe this is because in Afghanistan relative marriage is more custom than in Iran. And this issue increased the proportion of family epilepsy. The average age at the onset of seizures in patients was 4.11 ± 3.06. A review of 10 studies reported age at onset of epilepsy as a risk factor. The pooled ORs for age at onset of epilepsy were 7.03 (95% CI 3.30-14.98) and 5.49 (95% CI 2.99-10.06) [20]. In this study, there was a negative correlation between the onset of seizure and age, younger aged epileptic children's percentage was more than older categories of age.

The average duration of the disease in children in this study was 5.9 ± 2.21 years. In a study done in Toronto Canada, the average duration of epilepsy was 5.5 ± 3.9 years [18]. Their finding shows younger age than our study.

Patients were studied by the number of attacks, frequent seizures were observed in 41 (45.6%) of all patients, with 11 (12.2%) boys and 2 (2.2%) girls suffering from multiple seizures almost daily. As was found in a study which was done in Egypt, a higher number of males had frequent seizures [21].

When analyzing the types of seizures in patients with epilepsy, generalized seizures prevailed in frequency. 51 (56.7%) had primary generalized seizures (absences, myoclonic, atonic, infantile spasms) and in the study which was done in Spain, the percentage of generalized seizures was 52% which is near to our finding [22]. Also in a study which was done in Iran, the proportion of generalized seizures was found 72% in children [23], this percentage is more than our finding.

In 23 patients pathological changes were revealed during neuroimaging in the form of moderate cortical-subcortical atrophies. 26 patients had small local atrophy and 32 patients had signs of ventriculomegaly (unilateral or bilateral) but 6 patients had developmental anomalies. Also in a study that was done by Berna s and her colleagues in 2013, they reported that there was a significant relation between MRI abnormality and epilepsy [24]. Of the patients who had successful therapy in this study were 48 (53.3%). But in a study, Linda kalilani and her colleagues found the percentage of epileptic children who had remission was estimated at 60-70% [25]. And 42 (46.7%) children and adolescents were without remission. As is seen in this study's results, it is different from their study finding. Also, a study which was done in Iran in 2013 reported that in that study the remission rate was 71% [14], this finding is different from our study finding. Maybe, it is because in Afghanistan the patients don't receive standard epileptic care. 28.9% (26) had drug resistance epilepsy and it was identified that 16.7% (15) of patients who were treated as resistant cases, were pseudo-resistant due to incorrect selection or incomplete dosage of antiepileptic drugs. Generally, childhood epilepsy studies showed lower incidence proportions (15%) for pharmaco-resistant compared to adult patients (30%) [25]. In a large cohort study

of newly diagnosed epilepsy patients followed in Glasgow, Scotland, for a minimum of two years, 36% were not free of seizures at the last year of follow-up [26-29] As it is compared with other studies this study finding show more resistant epilepsy in epileptic children in Afghanistan. Maybe because of low awareness of patients and society from DRE risk factors, and low access to equipped hospitals for mothers for delivery.

Complete cessation of seizures was observed as a result of optimization of monotherapy with the first-line AED. In a longitudinal cohort study, the seizure freedom rate was 45.7% in patients who used first-line antiepileptic which was much more than with other regimens [30,31]. In the study that was done in Italy, the researcher reported that almost half of patients with epilepsy were controlled by rational use of AED [27].

In the subgroup of patients with a true pharmaco-resistant course of epilepsy 28.9% (N = 26), the average age of children at the time of the last visit was 11.15 ± 4.11 years. And the average age of children was 11.8 + 3 years in the study which was done by Lauryn Conway and her colleague in Toronto – Canada in 2016 [18], which was almost the same.

The epileptic children who participated in this research were studied by the difference between the type of seizures and having status epilepsy. This difference was found statistically significant (P-value < 0.0001). Primary generalized and secondary generalized seizures were with status epilepsy but two other categories were not. As there is shown in (Table 2) 66.7% of epileptic children experienced status epilepsy during their epilepsy, so the finding of this study is concordant with other studies. Also, Xue ping and colleagues reported in their study that having status epilepsy is a risk factor for refractory epilepsy and the relation was significantly positive [28].

The relationship between seizure types was studied with risk factors, the seizure types show a difference in risk factors. As it is illustrated, the p-value is less than 0.05 and shows significance. The difference between types of seizures and perinatal pathology, including traumatic brain injury, hereditary predisposition for epilepsy, and febrile seizures is statistically significant. Also, a study done in China in 2019 reported significant relation between primary generalized seizure and febrile seizure as well [28]. And in the study done in Sydney, Australia in 2014, there was a significant difference between seizure tapes by hereditary and genetic predispositions [29]. So, it is almost the same as this study's findings.

We have some recommendations and some limitations to doing this research.

Increasing the awareness of society of risk factors of epilepsy. Educating the health workers about the development of drug-resistant epilepsy in epileptic patients. Encouraging the policymakers to establish a supporting organization for epileptic patients in Afghanistan. There is a need for more research in this area, especially cohort studies in Afghanistan. The limitation of this study was, that our patient didn't have access to mobile and serial Electroencephalography so we used inter-ictal EEG of epileptic children.

Conclusion

A comprehensive clinical and neurophysiological examination of epileptic children made it possible to draw the following conclusions:

This research will contribute to expanding knowledge about epilepsy. This indeed is the first study to evaluate epileptic patients in the Herat city of Afghanistan. The knowledge related to epilepsy is low in Afghanistan, such as information about the risk factors of epilepsy. This study will help and highlight to all (policymakers, health workers, epileptic patients, and their families) to increase their knowledge about epilepsy and its risk factors. To the finding of this study and other pieces of evidence, the public health of Afghanistan can organize activities to decrease the prevalence and incidence of epilepsy. If the risk factors like perinatal trauma and injuries that were identified as one the important risk factors in the west zone of Afghanistan reduces by equipped hospitals for women's delivery, it will help much and will decrease the epilepsy incidence. Also, in this study, another risk factor was found which was more prevalent among the study participant was hereditary predisposition, by educating and increasing the awareness of society the risk of genetic diseases can be reduced.

This study also helps to identify the early prognostic factors that can be used as preventive factors. These factors are mentioned in world literature as well, as the number of seizures in epileptic children, epilepsy with high frequency, abnormal electroencephalography findings, and early onset of epilepsy can be risk factors for refractory epilepsy. Which were evaluated in this study and their result are shown.

References

1. Shorvon SD, Andermann F, Guerrini R. 2011. The causes of epilepsy. Cambridge University Press, Cambridge.
2. Asadi-PooyaA, Sharifzade M. Lennox–Gastaut syndrome in south Iran: Electro-clinical manifestations. Seizure. 2012; 21:760–763. [PubMed] [Google Scholar]
3. Robert S. Fisher, †Carlos Acevedo, ‡Alexis Arzimanoglou, §Alicia Bogacz, Helen Cross, Christian E. Elger, Jerome Engel Jr, Lars Forsgren, Jacqueline A. French, Mike Glynn, Dale C. Hesdorffer, B.I. Lee, Gary W. Mathern, Solomon L. Moshe, Emilio Perucca, Ingrid E. Scheffer, Torbjorn Tomson, Masako Watanabe, and Samuel Wiebe, A practical clinical definition of epilepsy. Epilepsia, 55(4): 475–482, 2014, doi:10.1111/epi.12550
4. Berg AT. Epilepsy, Cognition, and behavior: The clinical picture. Epilepsia 2011; 52: 1-12
5. Kalilani L, Sun X, Pelgrims B, Noack-Rink M, Villanueva V. The epidemiology of drug-resistant epilepsy: A systematic review and meta-analysis. Epilepsia. 2018. 13 November 2018. https://doi.org/10.1111/epi.14596
6. Zhibin Chen, PhD; Martin J. Brodie, MD; Danny Liew, MD, PhD; Patrick Kwan, MD, PhD, Treatment Outcomes in Patients With Newly Diagnosed Epilepsy Treated With Established and New Antiepileptic Drugs, A 30-Year Longitudinal Cohort Study, JAMA Neurol. 2018; 75(3):279-286. doi:10.1001/jamaneurol.2017.3949
7. World Health Organization. Epilepsy. Fact sheet. No. 999. 2012. UpdatedFebruary2016.http://www.who.int/mediacentre/factsheets/fs999/en/. Accessed March 12, 2016.
8. WHO global report on epilepsy, 20 June 2019 https://www.who.int/news-room/fact-sheets/detail/epilepsy
9. Robert S. Fisher, †Carlos Acevedo, ‡Alexis Arzimanoglou, §Alicia Bogacz, Helen Cross, Christian E. Elger, Jerome Engel Jr, Lars Forsgren, Jacqueline A. French, Mike Glynn, Dale C. Hesdorffer, B.I. Lee, Gary W. Mathern, Solomon L. Moshe, Emilio Perucca, Ingrid E. Scheffer, Torbj€orn Tomson, Masako Watanabe, and Samuel Wiebe, A practical clinical definition of epilepsy. Epilepsia, 55(4): 475–482, 2014, doi:10.1111/epi.12550
10. Rowland NC, Englot DJ, Cage TA, et al. A meta-analysis of predictors of seizure freedom in the surgical management of focal cortical dysplasia. JNeurosurg 2012; 116:1035–1041.
11. http://www.ncbi.nlm.nih.gov/pubmed?term=Prevalence of childhood epilepsy in Canada
12. Geithner J, Schneider F, Wang Z, et al. Predictors for long-term seizure outcome in juvenile myoclonic epilepsy: 25–63 years of follow-up. Epilepsia 2012; 53:1379–1386
13. Rowland NC, Englot DJ, Cage TA, et al. Ameta-analysis of predictors of seizure freedom in the surgical management of focal cortical dysplasia. JNeurosurg 2012; 116:1035–1041.
14. Kim JH. Grey and White Matter Alterations in Juvenile Myoclonic Epilepsy: A Comprehensive Review. J Epilepsy Res. 2017 Dec 31;7 (2):77-88. doi: 10.14581/jer.17013.
15. Quintas R, Alvarez AS, Koutsogeorgou E, et al. The relationship between health-related quality-of-life and disability in patients with controlled epilepsy: a cross-sectional observational study. Am J Phys Med Rehabil. 2012; 91: S31–8
16. Campos G, Fortuna A, Falcão A, Alves G (2018) In vitro and in vivo experimental models employed in the discovery and development of antiepileptic drugs for pharmaco-resistant epilepsy. Epilepsy Res 146:63–86
17. Seneviratne U, Hepworth G, Cook M, D'Souza W. Atypical EEG abnormalities in genetic generalized epilepsies. Clin Neurophysiol 2016; 127:214–220
18. Poduri A, Lowenstein D. 2011. Epilepsy genetics – Past, present, and future. Curr Opin Genet Dev 21: 325–332
19. Kim H, Paige AL, Knowlton RC. 2010. Advances in structural and functional neuroimaging: How are these guiding epilepsy surgeries. In Epilepsy: Mechanisms, models, and translational perspectives (ed.RhoJM, SankarR, Stafstrom CE), pp. 257–282. CRC, Boca Raton, FL
20. Wang Xue-Ping, MD, Wang Hai-Jiao, MD, Zhu Li-Na, MD, Da Xu, MD, and Liu Ling, MD- Risk factors for drug-resistant epilepsy, A systematic review and meta-analysis. Medicine (Baltimore). 2019 Jul; 98(30): e16402. Published online 2019 Jul 26. doi: 10.1097/MD.0000000000016402
21. Chem Z, Brodie MJ. Kwan P, Liew D, treatment outcomes with newly diagnosed epilepsy treated with new antiepileptic drugs. JAMA Neural 2018. Doi:10.1001
22. Gururaj A, Sztriha L, Hertecant J, et al. Clinical predictors of intractable childhood epilepsy. J Psychosom Res. 2006; 61:343–7
23. Lauryn Conway, Mary Lou Smith, Mark A. Ferro,§Kathy N. Speechley, Mary B. Connoly, O. Carter Snead, **Elysa Widjaja. Correlates of health-related quality of life in children with drug resistant epilepsy and the PEPSQOL Study Team1 Epilepsia,1–9,2016 doi:10.1111/epi.13441
24. Peter Camfield, Carol Camfield Dalhousie. Incidence, prevalence and aetiology of seizures and epilepsy in children. University and IWK Health Centre, Department of Pediatrics, Halifax, Nova Scotia, Canada Received September 25, 2014; Accepted February 08, 2015
25. Balan S, Bharathan SP, Vellichiramal NN, Sathyan S, Joseph V, Radhakrishnan K, et al. (2014) Genetic Association Analysis of ATP Binding Cassette Protein Family Reveals a Novel Association of ABCB1 Genetic Variants with Epilepsy Risk, but Not with Drug-Resistance. PLoS ONE 9(2): e89253. https://doi.org/10.1371/journal.pone.0089253
26. Berna S Y MD, Cetin O MD, Mustafa K MD. Predictors of intractable Childhood Epilepsy. http://dx.doi.org/10.1016/j.pediatrneurol.2012.09.008
27. Kourosh S, PhD,1,2 Hamed T, BS,3 Fatemeh S, MS,3 Iman M, BS,3 and Kristin V. C, MD, PhD. Prevalence of Epilepsy in Iran: A Meta-Analysis and Systematic Review. Iran J Child Neurol. 2014 Autumn; 8(4): 9–17
28. Valizadeh L, Barzegar M, Akbarbegloo M, Zamanzadeh V and et al. the relationship between psychological care and attitudes toward illness in adolescents with epilepsy. Elsevier, 28 February 2013
29. Isabella G, Aglaia V, Elisa V, Marina C, Laura C, Valentina C, Elena G, Francesca La B, Ferruccio P. Focal epilepsies patients attending two epilepsy centers: Classification of drug-resistance, assessment of risk factors, and usefulness of "new" antiepileptic drugs. Epilepsia, First published: 23 February 2012 https://doi.org/10.1111/j.1528-1167.2012.03416.x
30. Kishk, N., Mourad, H., Ibrahim, S. et al. Sex differences among epileptic patients: a comparison of epilepsy and its impacts on demographic features, clinical characteristics, and management patterns in a tertiary care hospital in Egypt. Egypt J Neurol Psychiatry Neurosurg 55, 39 (2019). https://doi.org/10.1186/s41983-019-0078-7
31. Haidery, A. The prevalence of drug-resistant epilepsy in 7-18 years old epileptic children in west zone of Afghanistan. 2021.

IRSTI 76.29.34: https://doi.org/10.26577/IAM.2022.v3.i2.02

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RETROSPECTIVE ANALYSIS OF GASTRITIS ASSOCIATED WITH CHRONIC ATROPHIC H. PYLORI IN PATIENTS WITH NOCARDIAL GASTRIC CANCER IN BUKHARA CITY AND PREVENTION OF ATROPHIC PROCESSES OF GASTRIC MUCOSA

Atrophic gastritis is understood as a progressive inflammatory process of the gastric mucosa, characterized by the loss of gastric glands. Helicobacter pylori infection (HP) and autoimmune gastritis are recognized as the most common etiological factors causing atrophic gastritis. The results of a retrospective analysis of the prevalence of chronic atrophic gastritis associated with H. pylori in patients with non-cardiac gastric cancer in Bukhara city were described. In addition, an algorithm for early diagnosis of atrophic processes of the gastric mucosa has been developed. When the incidence rate of chronic atrophic gastritis associated with H. pylori was analyzed in patients with non-cardiac gastric cancer in the city of Bukhara, it was noted that it tended to increase for 5 years from 2015 to 2019. Based on the research results, a personal algorithm for the formation of risk groups of atrophic processes of the gastric mucosa was developed. A personalized algorithm allows forming risk groups for atrophic processes of the gastric mucosa based on serological parameters, as well as taking into account data on genetic predisposition.

Keywords: chronic atrophic gastritis, gastric mucosa, H. pylori, non-cardiac gastric cancer.

Introduction

Atrophic gastritis is an urgent problem of modern gastroenterology in our country and around the world as it may transform into gastric cancer [1, 2]. The clinical and morphological feature of atrophic gastritis is a decrease in the number of specialized glandulocytes that provide secretory function of the stomach, and their replacement with simpler cells, including those that produce mucus. Extensive atrophy of the mucous membrane of the body of the stomach, as a rule, is associated with hyposecretion of hydrochloric acid and impaired pepsinogen production [3, 4]. Moreover, the occurrence of the vast majority of atrophic gastritis is associated with Long-existing superficial H. pylori gastritis is transformed into atrophic without appropriate treatment [5, 6].

Atrophic gastritis clinically, as a rule, does not manifest itself for a long time, therefore, the diagnosis of chronic gastritis is more morphological than clinical [7, 8]. Gastric cancer (GC) is a global health burden and the fourth most common cause of death from cancer in the world. A sequential histopathology cascade for the development of gastric adenocarcinoma of the intestinal type – from normal gastric epithelium to chronic gastritis, chronic atrophic gastritis (CAG) and intestinal metaplasia (IM), followed by dysplasia and, finally, GC. Patients with precancerous diseases, such as CAG or dysplasia, have a significant risk of developing cancer, and early detection of these lesions is important for screening for cancer [8, 9]. For CAG population screening, the endoscopic mass screening program has been shown to be effective in countries with a predominant GC, such as Korea and Japan. Overview of modern concepts of gastric metaplasia and gastric cancer. An endoscopic screening program reduced mortality rate associated with cancer by 47% as part of a case-control study in Korea. The effectiveness of the Korean National Cancer Program in reducing stomach cancer mortality [10].

The aim of the study was to study the endoscopic and morphological features of the mucous membrane of the stomach and intestines using the OLGA system in chronic atrophic gastritis.

Materials and Methods

During 2015-2019, a retrospective analysis of 152 patients diagnosed with non-cardiac gastric cancer was conducted at the Bukhara branch of the Republican Specialized Oncology and Radiology Scientific and Practical Medical Center based on their medical records and medical history. Based on the research results, a personal algorithm for the formation of risk groups of atrophic processes of the gastric mucosa was developed.

The results obtained during the study were subjected to statistical processing using SPSSv.15.0 (2007) and MS Excel software package for Windows

XR. The following values and criteria were calculated using standard methods of variation series: arithmetic mean value (M), arithmetic mean error (μ). Student's t-test was used to assess the statistical significance of differences between two selected indicators.

Results

According to the results of the analysis, the incidence of chronic atrophic H. pylori-related gastritis in patients with non-cardiac gastric cancer was 66.1% in 2015, 68.9% in 2016, 69.1% in 2017, and 69.1% in 2018. – 68.6%, in 2019 – 69.5%.

Detection of atrophic changes of the gastric mucosa during preventive medical examinations in the city of Bukhara is very low, in 2015 it was 0.3%, and in 2019 it increased to 3%, which may be related to the beginning of the widespread use of EFGDS along with biopsy in people at risk.

The gender distribution of chronic atrophic H. pylori-associated gastritis in patients with non-cardiac gastric cancer revealed an annual increase in the number of men and a decrease in the number of women. Thus, in 2015, the number of men and women with non-cardiac gastric cancer was 68.4% and 32.6%, respectively, and in 2019, it was 72.8% and 27.2%.

The most common chronic atrophic H. pylori-associated gastritis in patients with non-cardiac gastric cancer was found at the age of 50-65 years, in women at the age of 66-80 years. It should be noted that individual cases of this pathology occurred at the age of 25-35 years, which indicates a younger age of atrophic changes in patients with non-cardiac gastric cancer.

According to WHO recommendations, H. pylori is the first factor of carcinogenesis. Bukhara region is one of the regions with high prevalence of H. pylori. Accordingly, the incidence of non-cardiac gastric cancer in these regions may be directly related to the prevalence of H. pylori. Therefore, in our study conducted in the city of Bukhara, a high incidence of chronic H. pylori-associated atrophic gastritis was found in patients with non-cardiac gastric cancer.

Preventing the formation of atrophic processes of the gastric mucosa

Based on the results obtained during the study, a personal algorithm for the formation of risk groups of atrophic processes of the gastric mucosa was developed. According to this algorithm, risk groups were divided into 3: low, medium and high risk of atrophic processes of the gastric mucosa.

Low risk group of atrophic processes of the gastric mucosa

In the low-risk group, if H. pylori is negative, pepsinogen I, pepsinogen II, pepsinogen I / pepsinogen II is normal, if there is no genetic predisposition to non-cardiac gastric cancer, if he does not smoke, if he does not consume high-salt products, he is considered as a healthy stomach, and EFGDS is not necessary. If H. pylori (+), pepsinogen I, pepsinogen II, pepsinogen I/pepsinogen II are normal or increased, chronic H. pylori-associated nonatrophic gastritis, if H. pylori (+), pepsinogen I is increased; pepsinogen II, pepsinogen I / pepsinogen II normal or increased, with frequent use of nonsteroidal anti-inflammatory drugs, there is a risk of erosive ulceration of the stomach and duodenum, and in both cases, erdicative therapy is necessary. And EFGDS is prescribed according to the guidelines, ie, smoking, hereditary predisposition to non-cardiac gastric cancer and intake of high-salt products (Figure 1).

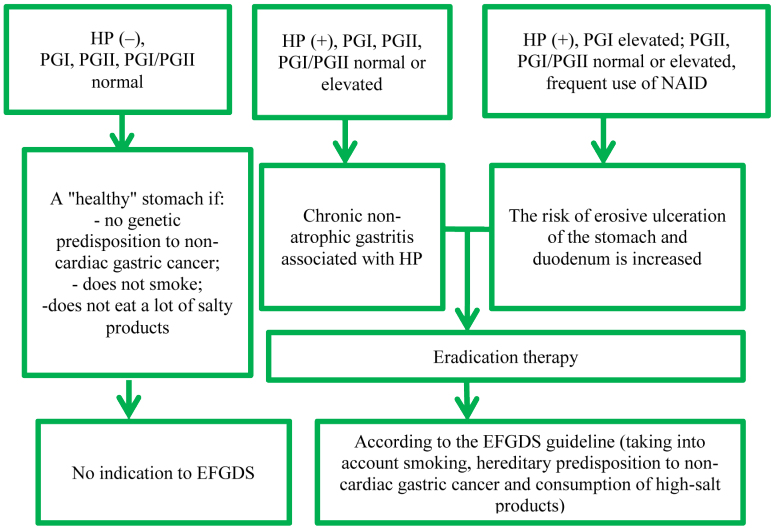

Figure 1 – Low risk of atrophic processes of the gastric mucosa

In the risk group, if HP+, PGI 11-30 µg/l and PGI/PGII – 2.1-3, HP is evaluated as associated slow or significant atrophic gastritis, in which eradication therapy is necessary, if the patient has a hereditary predisposition to non-cardiac gastric cancer. and if he eats a lot of salty products, EFGDS is performed along with multifocal biopsy, and according to OLGA, it is evaluated as gastritis level 1 or 2 (Fig. 2).

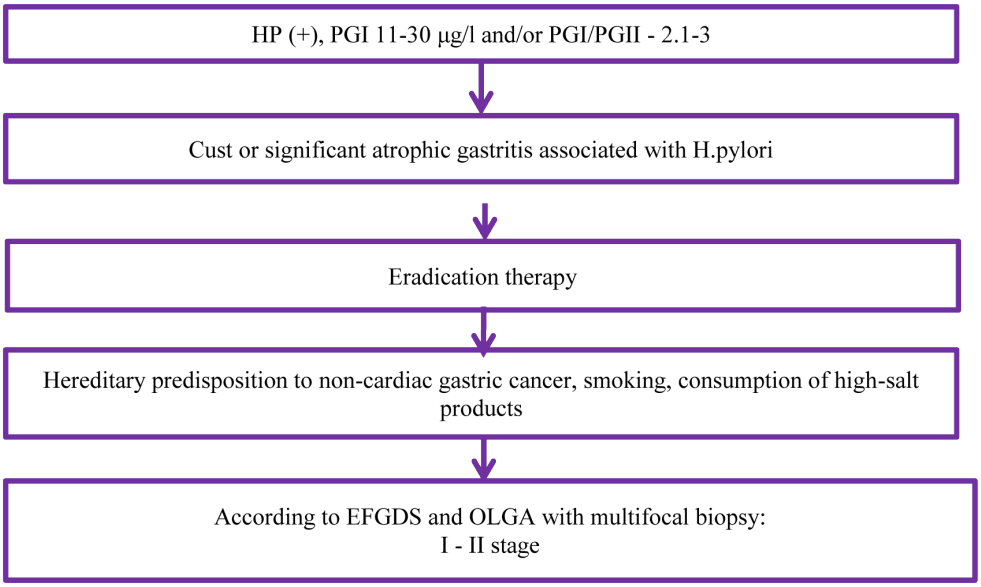

Figure 2 – Average risk of atrophic processes of the gastric mucosa

In the high-risk group, regardless of whether HP (+) or HP (-), PG I is less than 10 µg/l and PGI/II is less than 2, it is evaluated as a single atrophic gastritis, eradication therapy is necessary, if the patient has a history of non-cardiac gastric cancer If there is a tendency to eat a lot of salty products, EFGDS is performed along with multifocal biopsy, and according to OLGA, it is estimated as 3 or 4 stages of gastritis (Fig. 3).

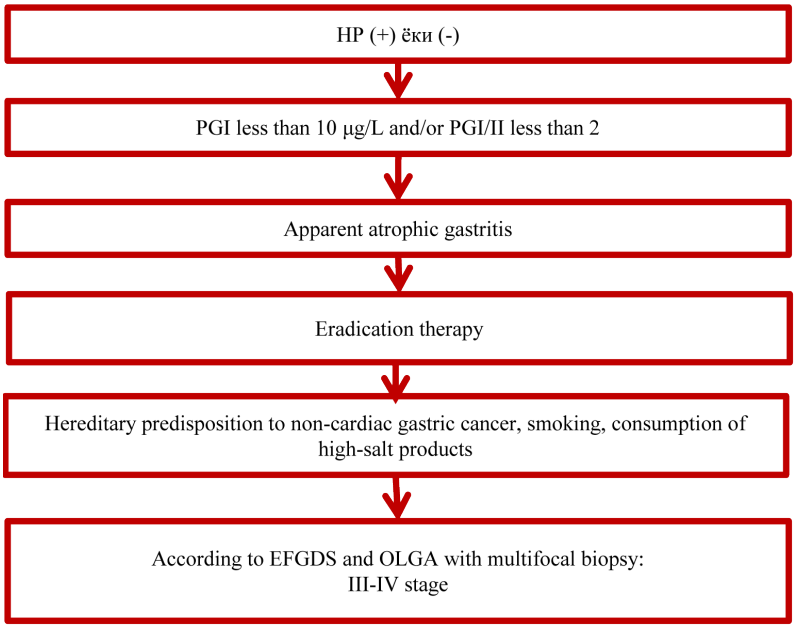

Figure 3 – High risk of atrophic processes of the gastric mucosa

Thus, a personalized algorithm allows forming risk groups for atrophic processes of the gastric mucosa based on serological parameters, as well as taking into account data on genetic predisposition. People diagnosed with atrophic processes of the gastric mucosa require observation using endoscopic and morphological studies.

Discussion

To date, there is a certain understanding of the serological diagnosis of atrophic processes of the gastric mucosa in the world. Over the years, studies by various authors have confirmed that atrophic fundal gastritis can be successfully determined by serum pepsinogen-I or the ratio of pepsinogen-I to pepsinogen-II. It has been shown that serological screening using a set of biomarkers can serve as an early indicator of pre-tumor pathology and gastric cancer [16]. Thanks to national cancer control programs and mass screening, which includes serological methods, Japan has the highest stomach cancer survival rate in the world at 53%, compared to less than 20% in other countries. At the same time, the proportion of early cancer detected in the total composition of patients with gastric cancer is increasing [7].

A number of results have been achieved in research conducted in the world to study the early diagnosis of atrophic processes of the gastric mucosa, including: it was found that the low level of pepsinogen-I and pepsinogen-I / pepsinogen-II are predictive for the risk of gastric cancer [8]; it was found that the method of early detection of atrophic gastritis through the level of pepsinogens allows to reliably determine the presence of atrophy of the gastric body and assess its severity [8]; mass screening of gastrin – 17 and pepsinogen – I serological markers has been proven to create an opportunity to characterize the risk of atrophy of the gastric mucosa [9]. It has been found that the use of serum biomarkers such as IgG antibodies, pepsinogens produced against H. pylori can reduce the cost of gastric cancer screening and the public health burden [10].

Conclusion

In the program developed for the early diagnosis of atrophic processes of the gastric mucosa, CAG risk factors are listed, each indicator is evaluated with points, and the severity of atrophy is determined based on the total sum. According to this algorithm, risk groups are divided into 3: with low, medium and high risk of atrophic processes of the gastric mucosa. Thus, if there is a low risk of atrophic processes of the gastric mucosa, EFGDS is performed based on the doctor's decision and taking into account the anamnesis and the clinic. At moderate and high risk of atrophic processes of the gastric mucosa, it is recommended to conduct a large number of biopsies with EFGDS and subsequent stratification of the risk of atrophic processes of the gastric mucosa taking into account the morphological systems OLGA and OLGIM. If H. pylori are detected, eradication therapy is necessary.

In conclusion, it can be said that based on these results, serological methods are compatible with morphological methods in terms of their diagnostic value. But in patients, if the atrophic processes are at the 2-3 level, nothing can replace the morphology. Serological methods can be used for screening or observation of patients with mild forms of gastritis, i.e., non-atrophic gastritis or slow or significant atrophy of atrophic gastritis.

References

1. Abdullaeva U.K. Predicting the risk of atrophic transformation in gastritis associated with chronic Helicobacter pylori // abstract of PhD dissertation on medical sciences. – Tashkent. 2021. – 46 p.

2. Abdullaeva U.K. Predicting the risk of atrophic transformation in chronic gastritis using serum pepsinogen // World journal of pharmaceutical research, Faculty of Pharmacy Medical University, Bulgaria. – Vol. 8, Iss. 13. – 2019, – P. 219-228.

3. Abdullaeva U.K., Sobirova G.N., Karimov M.M., Aslonova I.J. The prevalence and possibilities of prevention of noncardial gastric cancer in the Bukhara region // American journal of medicine and medical sciences. – 2020, 10(9). – P. 679-681.

4. Sobirova G.N., Abdullaeva U.K., Nosirova M.S., Aslonova I.J. Evaluation of the gastrointestinal mucosa by the OLGA system in chronic atrophic gastritis // Journal of critical reviews, Kuala Lumpur, Malaysia. – Vol. 7, Iss. 2, – 2020. – P. 409-413.

5. Dinis-Ribeiro M., Kashin S.V., Kuvaev R.O., Nadezhin A.S. et al. // Draft Recommendations of the Russian Endoscopic Society for Endoscopists, Gastroenterologists, Therapists, Oncologists and Surgeons. – 2012. – No. 44. – P. 74–94.

6. Sugano K., Tack J., Kuipers E.J. et al. Kyoto global consensus report on Helicobacter pylori gastritis // Gut. – 2015. – Vol. 64 (9). – P. 1353-1367.

7. Sun X., Bi Y., Nong B., et al. Linked color imaging confers benefits in profiling H. pylori infection in the stomach. // Endosc Int open. – 2019;7(7): E885–92.

8. Syrjänen K. A Panel of Serum Biomarkers (GastroPanel®) in Non-invasive Diagnosis of Atrophic Gastritis. Systematic Review and Meta-analysis // Anticancer Res. – 2016. – Vol. 36 (10). – P. 5133–5144.

9. Takeda T., Asaoka D., Nojiri S., et al. Linked color imaging and the Kyoto classification of gastritis: evaluation of visibility and inter-Rater reliability. // Digestion. – 2019:1–10.

10. Telaranta-Keerie A., Kara R., Paloheimo L. et al. Prevalence of undiagnosed advanced atrophic corpus gastritis in Finland: an observational study among 4,256 volunteers without specific complaints // Scand J Gastroenterol. – 2010. – Vol. 45. – P. 1036-1041.

IRSTI 76.29.39: https://doi.org/10.26577/IAM.2022.v3.i2.03

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THE CHOICE OF SURGICAL TACTICS FOR THE CORRECTION OF A HIATAL HERNIA IN PATIENTS WITH CHOLELITHIASIS COMBINED WITH GASTROESOPHAGEAL REFLUX

Reported here are the results of the examination and surgical treatment of 70 patients with cholelithiasis combined with hiatal hernia, of which 36 patients being in the main group and 34 patients in the comparison group who were hospitalized and underwent surgery in the clinic between 2020 and 2022. Based on an in-depth comparative analysis of early and long-term results of surgical treatment it has been proven to improve the efficiency of surgical treatment of patients with cholelithiasis, combined with gastroesophageal reflux disease and hiatal hernia. According to different authors, hiatal hernia is combined with cholelithiasis in 8-12% of cases. Insufficient preoperative examination of this group of patients often leads to underdiagnosis of concomitant pathology requiring surgical correction, and to failure to perform the necessary surgical treatment in such cases. Many authors indicate that up to 11% of patients with cholelithiasis after cholecystectomy during re-examination have a clinic of gastroesophageal reflux disease refractory to conservative therapy and requiring surgical treatment. In practice, the tactics are chosen in a calculation method using the original formula. Thanks to the research, it was possible to optimize the tactics of surgical treatment of patients with comorbidities.

Keywords: cholelithiasis; hiatal hernia; gastroesophageal reflux disease; combined pathology.

Introduction

According to different authors, hiatal hernia (HH) is combined with cholelithiasis (GSD) in 8-12% of cases. Insufficient preoperative examination of this group of patients often leads to underdiagnosis of concomitant pathology requiring surgical correction, and to failure to perform the necessary surgical treatment in such cases [1, 2, 3, 4].

Many authors indicate that up to 11% of patients with cholelithiasis after cholecystectomy (CE) upon re-examination have a clinic of gastroesophageal reflux disease (GERD), refractory to conservative therapy and requiring surgical treatment [5, 6, 7].

Literature data show that HH relapses after surgical treatment of cholelithiasis, combined with GERD and HH, occur from 3 to 12%, and in the group of patients with a hiatal opening larger than 6 cm2 – up to 30%. One of the main causes of HH recurrence is tissue tension and dystrophic changes in the crura of the diaphragm. Suturing during crurorrhaphy on disintegrated, atrophically altered tissues in case of abiotrophy of the diaphragm crura, and large defects with significant tension, leads to eruption of the sutures, displacement of the fundoplication cuff to the posterior mediastinum and recurrence of HH or formation of a paraesophageal hernia [8, 9, 10].

Introduction of laparoscopic technologies enabled performing one-stage surgical interventions when cholelithiasis is combined with GERD and HH. Laparoscopic surgical interventions for the aforementioned pathology are less traumatic, provide good results in 88.5-94% of patients during follow-up periods of more than 10 years [11, 12]. However, despite the constant improvement of modern methods of diagnostic assessment and simultaneous surgical correction of this comorbidity, today there is neither single treatment strategy, nor the choice of the optimal method for correcting HH and GERD in cholelithiasis.

*Objective of the work***:** patients with cholelithiasis, combined with GERD and HH and to determine the optimal methods of surgical correction of the hernial defect.

Materials and Methods

The work is based on a clinical analysis of the results of examination and treatment of 70 patients suffering from GERD and HH in combination with cholelithiasis. The main group consisted of 36 patients who underwent simultaneous operations for HH and GERD combined with cholelithiasis using an advanced technique for choosing surgical tactics. In addition, original research has been performed in the setting of endoscopy and surgery department of the Bukhara Branch of the Republican Research Center of Emergency Medical Care between 2020 and 2022.

The control group included 34 patients with GERD and HH who had previously undergone laparoscopic cholecystectomy for cholelithiasis. All patients in the control group underwent laparoscopic surgical treatment of HH and GERD using current standards for choosing surgical tactics.

Distribution of patients by sex and age is similar to the one in the control and main groups. The age of the patients varied between 23 and 76. Among them prevailing were the females aged 40-60 and above (Table 1).

Table 1 – Distribution of patients by sex and age

Sex and age	Patients groups			
	Main group (N = 36)		Control group (N=34)	
Male	Abs	%	Abs	%
20-40 y.o.	1	2.8	3	8.8
40-60 y.o.	8	22.2	9	26.5
60 y.o. and above	6	16,7	4	11.8
Total	15	41,7	16	47,1
Females	Abs.	%	abs.	%
20-40 y.o.	4	11,1	4	11.8
40-60 y.o.	10	27.8	9	26.5
60 y.o. and above	7	19.4	5	14.6
Total	21	58.3	18	52.9

In the preoperative period the patients were examined in full according to the standard scheme, including complaints, history taking, physical examination, blood and urine tests, and instrumental research methods, including electrocardiography, lung radiography, abdominal ultrasound, esophagogastroduodenoscopy, radiopaque polypositional examination of the esophagus, stomach and duodenum.

When choosing a surgical tactic for HH correction in the main group, we were guided by the methodology developed at the department. This technique is based on the intraoperative determination of the complexity of the hiatal hernia correction in the form of a scoring of the corresponding coefficient according to the formula:

F = D+G+H+HAS, where:

F is HH correction complexity index;

D is the severity of duodenogastric reflux;

G is the severity of gastroesophageal reflux (GER);

H is the severity of HH;

HAS is a measure of the area of the hiatal opening.

Each indicator was evaluated on a point system as follows.

D – presence of duodenogastric reflux (endoscopically preoperatively): 0 points means no reflux;

1 point means there is reflux.

G is the severity of GER (endoscopically preoperatively):

No GER – 0 points;

1st degree – 1 point;

2nd degree – 2 points;

3rd degree – 3 points;

4th degree – 4 points;

H is the severity of HH (fluoroscopically preoperatively):

– 1st degree – 1 point;

– 2nd degree – 2 points;

– 3rd degree – 3 points;

HAS is the indicator of the area of the hiatal opening (intraoperatively):

– up to 4 cm^2 – 1 point;

– between 4 cm^2 and 8 cm^2 – 4 points;

– more than 8 cm^2 – 10 points.

HAS was calculated according to the method described by F.A. Granderath et al. in 2007, which consisted in intraoperative instrumental measurement of the length of the diaphragm crura (R, cm), the distance between the extreme points of the maximum distance between the crura of the diaphragm (S, cm) and the calculation using 4 formulas:

1) alpha 1=arcsin(S/2)/R;

2) alpha0=2×alpha 1;

3) B=π×R×alpha 0/180;

4) HAS=B×R/2,

Is an indicator equal to the value of arcsin – half the distance between the extreme points of the maximum distance between the crura of the diaphragm, divided by R – the length of the crura of the diaphragm in cm;

alpha 0 is an indicator equal to alpha 1 multiplied by 2;

B – radial index, calculated according to formulas of multiplication – the values of π (3.14) are multiplied by R – the length of the diaphragm crura and multiplied by the resulting value alpha 0 and divided by 180;

HAS is an indicator of the area of the hiatus opening (cm2), equal to the product of the obtained value B by half R.

Depending on the data obtained, the tactics of surgical correction of HH was chosen.

At F≤5, anterior crurorrhaphy was performed. At values of 5≤F≤12, posterior crurorraphy was performed.

At F>12 values, posterior crurorrhaphy and diaphragmocruroplasty were performed with a non-adhesive mesh explant.

After performing surgical correction of HH in patients of the main group, antireflux fundoplication was performed according to the original technique developed at the department using reinforcement of crurorrhaphy with the stomach wall.

Cholecystectomy was performed at the last stage using previously installed trocars.

In the control group, the choice of tactics for surgical correction of HH was based on the value of the area of the hiatal opening HAS.

At HAS values ≤4 cm2, crurorrhaphy was performed by placing 1-3 sutures on the crura of the diaphragm, whereas at HAS values between 4 cm2 and 8 cm2, crurorrhaphy was performed in combination with diaphragm cruroplasty using a mesh explant; at HAS values over 8 cm2, "Tension- free" plastics was performed which consists of diaphragm cruroplasty with a mesh explant.

Results and Discussion

All patients in the control group underwent laparoscopic cholecystectomy for cholelithiasis in various clinics and at various times over the past 10 years. The diagnosis of concomitant GERD and HH was established in 12 (35.3%) patients in the control group prior to LCE. In all these patients, reflux complaints intensified after LCE.

In the remaining 22 (64.7%) patients of the control group, targeted diagnostics of GERD and HH were not performed prior to LCE. However, all these patients had a history of characteristic reflux complaints prior to LCE, which also intensified in the postoperative period, which forced these patients to undergo endoscopic and radiopaque studies, upon which they were diagnosed with GERD and HH. Patients in the main group were most often diagnosed with stage II-III GERD associated with some I-II stage HH. The distribution of patients depending on the factors of choice of surgical tactics according to the original formula is presented in Table 2. In the control group, all patients underwent laparoscopic correction of esophageal hiatus with posterior crurorrhaphy supplemented by alloplasty – (table 2) 5 patients (14,7 %).

All operations in the group were combined with Nissen fundoplication (floppy) – in 16 (47.1 %) patients with II-III degree HH and Dora – Harrington in 18 (52.9 %) patients with stage I HH. In the main group, laparoscopic correction of HH was performed using anterior crurorrhaphy in 14 patients (38.9%), using posterior crurorrhaphy in 15 patients (41.7%), using combined anterior and posterior crurorrhaphy in 7 (19.4%) patients, supplemented by alloplasty in 4 (11.1%) patients. All operations in the main group were combined with fundoplication modified by the Department of Endoscopy and Surgery and ended (table 3) with cholecystectomy.

Table 2 – Distribution of patients in the main and control groups according to the factors of choice of surgical tactics

Patients groups		Main group (N = 36)		Control group (N=34)	
Factors		Qty	%	Qty	%
HAS	Less than 4 cm2	28	77.8	26	76.5
	4 – 8 cm2	5	13.9	6	17.6
	8 cm2 and >	3	8.3	2	5.9
GER severity	1st degree	**3**	**8.3**	**4**	11.8
	2nd degree	**12**	**33.3**	**13**	38.2
	3rd degree	**14**	**38.9**	**12**	35.3
	4th degree	**2**	**5.6**	1	2.9
HH severity	1st degree	24	66.7	20	17.7
	2nd degree	8	22.2	8	23.5
	3rd degree	4	11.1	5	14.7
Presence of DGR		32	88.9	31	91.2
F	Less than 5	22	61.1	25	73.5
	5-11	11	30.6	7	20.6
	>12	3	8.3	2	5.9

During the follow-up period of 2-5 years or more, it was revealed that in the main group of patients (N=36) there were no recurrences of GERD and HH. No complications were found in the postoperative period.

In the control group of patients (N=34), 2 (5.9%) relapses of GERD and HH were revealed followed by repeated laparoscopic surgical interventions with alloplasty of recurrent HH and floppy-Nissen fundoplication.

In 1 (2.9%) patient of the control group after laparoscopic HH alloplasty and Nissen fundoplication, dysphagia was observed with the formation of a stricture of the esophageal-gastric junction around application of the alloplasty cuff, which required several sessions of balloon dilatation.

The choice of surgical tactics in the control group was based upon the standard method for determining the area of the hiatus opening without considering the above factors.

According to the statistics calculations using the determination of Student's t-criterion, a statistically significant difference was found between the effectiveness of treatment in the main and control groups (significance level $p<0.05$).

It has been statistically confirmed that improved results of treatment of patients in the main group were reliable in comparison to the one in the control group In this regard we can say that the factors taken into account in the original formula for calculating the choice of surgical tactics involving treatment of combined pathology are of fundamental importance.

Table 3 – Results of treatment and further observation of patients

Group	Main (N=36)		Control (N=34)	
	Abs.	%	Abs.	%
Anterior cruroraphy	14	38.9	-	-
Posterior cruroraphy	15	41.7	34	100
Combined cruroraphy	7	19.4	-	-
Alloplasty of HH	4	11.1	5	14.7
Relapse of GERD and HH	-		2	5.9

Conclusions

1.Insufficient diagnosis, as well as underestimation of already obtained diagnostic reflux data in cholelithiasis, and failure to perform appropriate surgical correction of GERD in LCE leads to the progression of reflux symptoms and requires additional surgical intervention and additional anesthesia, respectively.

2.The presence of comorbidity (cholelithiasis with GERD and HH) requires a multifactorial approach to the choice of tactics of surgical treatment, taking into account the severity of GER and HH, the presence of DGR, bile and the area of the hernial orifice.

3.The developed method of laparoscopic surgical correction of GERD and HH in combination with cholelithiasis allows avoiding the development of "cuff", "mesh" and other postoperative complications.

4.Optimized tactics of simultaneous laparoscopic surgical interventions when cholelithiasis is combined with GERD and HH enabled improving the results of treatment of these patients by reducing early and late reflux complications, reducing relapses and improving the quality of life.

References

1. Grishin VN, Vorobey FV, Chur NN. Hernia of diaphragma esophageal foramen and gastroesophageal reflux disease. – Minsk: Vysheyshaya Shkola, 2007. – 212 p.
2. Nir Ubezky, Boaz Sagie, Andrei Keidar, Armir Szold Prosthetic mesh repair of large and recurrent diaphragmatic hernias // Surgical Endoscopy and Other Interventional Techniques December. – 2007, Number 21: p. 737-738.
3. Gastoenterology. Surgical disease. Manual for doctors/ed. Lazebnik LB, Shcherbakov. – M.: Special public house of medical books, 2012. – 544 p.
4. Pozdniakov B.V. et al. Fundamentals of operative surgery of external bile tracts. – StP.: ELBI – StP, 2011. – 384 p.
5. Chernekhovskaya NE, et al. Operative laparoscopia. – M.: medpress, 2010. – 192 p.
6. Anyshchenko VV, et al. Allocruroapplication as method of defect closing at hernia diaphragma esophageal foramen // Gerniology. – M.: medpractica – M., 2014. – N 4. – P. 8-9
7. Slavin LE et al. Complications of abdominal hernia. – M.: Profile, 2015. – 154 p.
8. Sazhin VP et al. Endoscopic abdominal surgery. – M.: GOETAR = Media, 2010.- 512 p.

9. J. Cameron. Atlas of operative gastroenterology. – M.: GOETAR – Media, 2009. – 512 p.
10. Prevalence of uninvestigated dyspepsia and gastroesophageal reflux disease in Korea: a population-based study using the Rome III criteria / B. H. Min, K. C. Xin, H. K. Jung [et al.] // Dig. Dis. Sci. – 2014. – Vol. 59, N 1. – P. 2721 – 2729.
11. Overdiagnosis of gastro-esophageal reflux disease and under diagnosis of functional dyspepsia in a USA community / C. Pleyer, H. Bittner, G. R. Locke [et al.] // J. Neurogastroenterol. Motil. – 2014. – Vol. 26, N 8. – P. 1163 – 1171.
12. Granderath F.A., Schweiger U.M., Pointner R.Tailoring the hiatal closure to the size of hiatal surface area // Surgical Endoscopy and Other Interventional Techniques. – December 2007, Number 21: p.542-548.

IRSTI 76.01 https://doi.org/10.26577/IAM.2022.v3.i2.04

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SATISFACTION OF DENTISTRY FACULTY STUDENTS OF KABUL UNIVERSITY OF MEDICAL SCIENCES FROM ONLINE LEARNING OF PHYSIOLOGY DURING COVID 19 PANDEMIC AND ITS ADVANTAGES AND DISADVANTAGES FROM THE STUDENT'S POINT OF VIEW

The demand for online and distance education has expanded dramatically around the world since the coronavirus disease 2019 (COVID-19) pandemic in early 2020.The COVID-19 pandemic has disrupted teaching in a variety of institutions, especially in medical schools. Electronic learning (e-learning) became the core method of teaching the curriculum during the pandemic. To evaluate student's satisfaction and to find the advantages versus disadvantages of online learning of physiology subject from student's perceptions during pandemic a qualitative analytical research designed, which carried out in Kabul University of Medical Sciences (KUMS) on sophomore students of stomatology, in this research a self-administered questionnaire was used for collecting data. After 3 weeks of only online teaching, this survey was conducted; data gathered from the survey were analyzed with routine statistical software. 48 sophomore students of stomatology faculty of KUMS answered the questions, which indicated that 72.9% of students were strongly support online learning via Google classroom, and 25% of students were moderately support and 2% of students were not support online learning via GC. And according student's perceptions, avoiding of time wastage, usability of learning material everywhere any time, and learning how to use technology is the advantages of online learning, and low internet speed with high cost, disability of practical works are the disadvantages of online learning of physiology subject.

Keywords: Learning, Online, Google Classroom, Pandemic, Covid-19.

Introduction

World Health Organization (WHO) has declared the novel coronavirus (COVID-19) outbreak a global pandemic on March 11, 2020 [1]. The first case was officially recorded, in the Wuhan City of China. Since then it gradually shifted to other part of the world and there has been substantial growth across the globe. The first case of COVID-19 in Afghanistan was stated in the province of Heart in a 35-year-old Afghan citizen who had come back from Iran. CO VID-19 was accountable for 69,130 confirmed case s and 2,881 deaths in the country as of May 28, 202 1These assessments, however, do not appear to correspond to the real rate of disease transmission [2]. Coronavirus pandemic has not only impacted human life but also impacted medical education and residency training all over [2-3]. With principles of social distancing, all face to face classes were suspended due to the ongoing COVID 19 pandemic [4]. According to UNESCO, by the end of April 2020,186 countries have implemented nationwide closures, affecting about 73.8% of the total enrolled learners [5].

Afghanistan government announced on 14 March, that all educational institutes in the country would not open until 21 April. And announced, that lessons would be taught online. Initially educational institutions one after another paid attention to facilitate educational materials for their students by using different applications. Kabul University of Medical Sciences «Abu Ali Ibn Sina» also decided to continue online courses by creating classes in the Google Classroom for different faculties, in order to avoid wasting students' time. Therefore, it is a new teaching method in Kabul University of Medical Sciences; the following research was launched in order to know the level of satisfaction and pros and cons of online learning from students' perspective. Numerous studies show that online teaching method is effective, for example Mohammad Taghi Mohammadi and his colleagues found that online teaching of physiology online is effective and increases students' creativity [6]. In another study which conducted in 2018 by Diane O Doherty and his colleagues found that lack of technical skills, inadequate facilities, lack of specific online teaching strategy and, time constraints

are one of the major obstacles to launching online teaching in medical education [7]. Izwan Nizal and his colleagues in Malaysia found that students were more satisfied with teaching in the Google Classroom. This research was conducted on over 100 students who were taught by using Google classroom application [8]. Lubna Salamat and his colleagues found that online education has no time limitation and they feel relax and enable students to solve problems without the help of others [9]. Leisi Pei and her colleague found that online teaching compared to offline teaching is effective in improving students' knowledge [10].

Objectives

– To find students satisfaction from online teaching method using Google classroom;

– To find pros and cons of online teaching method from student point of view;

Major Research questions

– Are students satisfied from online teaching method in physiology?

– What are the pros and cons of teaching online in physiology from student point of view?

Material and Methods

This is a cross sectional study was conducted at Kabul University of Medical Sciences "Abu Ali Ibn Sina" Sample number: Second grad students of dentistry faculty of KUMS, who's joining to Google classroom. N=87

It was a qualitative analytical study, which is done to second grade students of dentistry faculty of Kabul University of Medical Sciences. According to the curriculum of student's cardiovascular physiology has been taught online by using of Google classroom application by sending of videos which created with Camtasia studio 8 and PowerPoint slides. Then a self-administered questionnaire is sent via Google classroom to the students for obtaining data and students response sheet were collected via Email. Data gathered from the survey were analyzed with routine statistical software.

Inclusion criteria second grad students of dentistry faculty of KUMS, who's joining to Google classroom N=87.

Expulsion criteria. Students of other grads of Kabul University of Medical Sciences "Abu Ali Ibn Sina"

Major research variables

– Independent variable: online teaching method

– Dependent variable: Students opinion about online teaching method

Research tools and data collection source: The data obtained from students is a primary data and collected from questionnaires.

Results

In this study 48 students of second grad, dentistry faculty of KUMS were participated. After evaluating and analyzing the questionnaires, which indicated that 72.9% of students were satisfied with the online teaching method via (Google Classroom). And 25 percent of the students are relatively satisfied and 2 percent are not satisfied to learn through online. 91.6% of students were indicated that the quality of the submitted materials (graph 1) were high enough. And 97.9% of students were satisfied from mythology of teaching by their instructor.

Advantage of online teaching method from student's point of view are summarized as follow:

– Preventing time wastage;

– Usage of Google Classroom is easier than other online teaching methods;

– Familiarization of students with advanced technologies;

– Availability of course materials at any time anywhere for students;

– Avoiding of unnecessary consumption like transportation and food;

– Asking questions freely from instructors;

Disadvantage of online teaching method from student's point of view are summarized as follow:

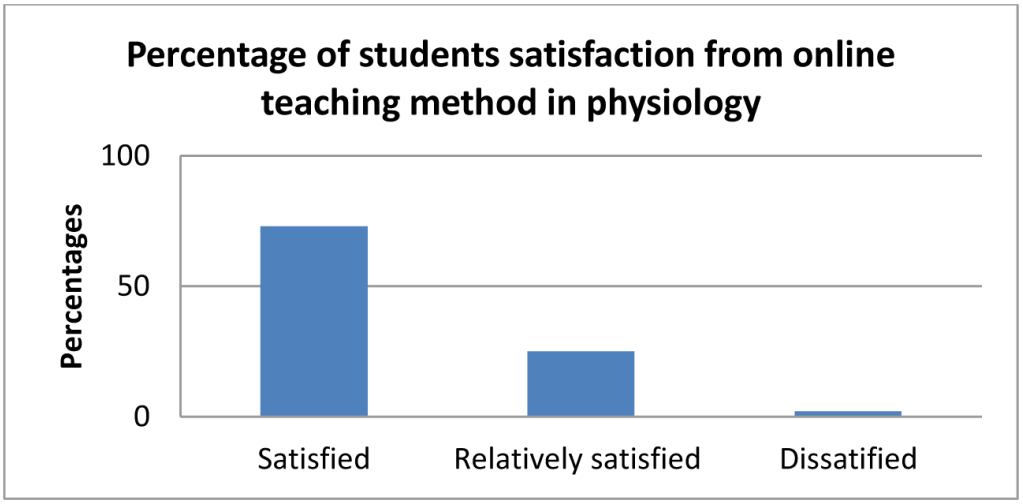
– Low speed and high cost of internet;

– Disability of practical works;

– Disability of instructors to evaluate students properly;

– Problems in downloading course materials;

– Time consuming to receive instructors reply;



Graph 1 – Shows the percentage of students' satisfaction from online teaching method in second grad faculty of dentistry KUMS

Discussion

Universities are continuously trying to deliver high quality teaching and consistent communication to students during these uncertain times. This new situation will be crucial in the coming times and this survey research has found some of the crucial result which help Universities to develop strategies. Overall the responses were positive towards the online learning. Based on the results yielded by the present study, implementation of online teaching improves knowledge of students and they strongly support online learning of physiology subject. And according students perceptions, Preventing time wastage, Familiarization of students with advanced technologies, Availability of course materials at any time anywhere for students, Avoiding of unnecessary consumption like transportation and food and Asking questions freely from instructors is the advantages of online learning, and low speed and high cost of internet, Disability of practical works, Disability of instructors to evaluate students properly, Problems in downloading course materials and Time consuming to receive instructors reply are the disadvantages of online learning of physiology subjects.

Because Afghanistan is one of those countries whose educational infrastructures is not fully mature, online teaching was faced with some problems, lack of familiarity of teachers and students with technology and the use of educational applications was among problems that fortunately solved as soon as possible.

Internet low speed and high cost was another problem that students faced. Fortunately, students endured this problem with great efforts and continued their studies.

Numerous studies have been conducted on various aspects of online teaching, and found that online teaching of Physiology online is effective and increases students' creativity [6]. Izwan Nizal and his colleagues in Malaysia found that students were more satisfied with teaching in the Google Classroom which was conducted on over 100 students who were taught by using Google classroom application [8]. Another study found that the average score of students who were taught online are higher than the average score of students who were taught by traditional lecture [11].

In fact, that this research shows the result of online teaching only in Physiology subject, which was done on a small number of students, therefore more comprehensive research is needed in this field.

Conclusion

Based on the results yielded by the present study, implementation of online teaching improves knowledge of students and they strongly support online learning of physiology subject during pandemic. Therefore, executives of education system should consider incorporation of online teaching in teaching-learning processes.

References

1. Mousavi, S., et al., The first COVID-19 case in Afghanistan acquired from Iran. The Lancet Infectious Diseases, 2020. 20.
2. Oria, M. S., Wardak, F. R., Rasib, A. R., Pirzad, A. F., Khel, M. I. I., Shefaye, H., & Negin F. (2022). Perceived Stress levels among Anaesthesia and Intensive Care staff during the third wave of the COVID-19 pandemic: A report from Afghanistan. Update in anaesthesia, 36, 86-96.
3. Chick RC, Clifton GT, Peace KM, Propper BW, Hale DF, Alseidi AA, Vreeland TJ. (2020). Using technology to maintain the education of residents during the COVID-19 pandemic. J Surg Educ.
4. Ferrel MN, Ryan JJ. (2020). the impact of COVID-19 on medical education. Cureus; 12:e7492.
5. United Nations Educational, Scientific and Cultural Organization. (2020). COVID-19 educational disruption and response.
6. Mohammdi, MT. Malik, S. Sanisales, Z. (2015). The impact of E- Learning on Creativity and learning in physiology course in Nursing Students of Shahrekord University of Medical Sciences. Future of Medical Education Journal; 5(4): 25-29.
7. Doherty, D. Dromy, M. Lougheed, J. Hannigan, A. Last, J. McGrath, D. (2018). Barriers and solutions to online learning in medical education- an integrative review. BMC Medical Education;18 (130).
8. Nizal, I. Jastani, MJ. Samimi, S. (2016). The Application of Google Classroom as Tool for Teaching and Learning. Journal of Telecommunication, Electronic and Computer Engineering; 8(10). e- ISSN:2289-8131
9. Salamat L, Ahmad G, Bakht MI, Saifi IL. Effects of e-learning on students' academic learning at university level. Asian Innovative Journal of Social Sciences and Humanities. 2018 Apr;2(2):1-2.
10. Pei, L. Hongbin, Wu. (2019) Does online learning work better than offlinelearning in undergraduate medical education.A systematic review and meta-analysis, Medical Education Online, 24:1, 1666538, DOI: 10.1080/10872981.2019.1666538
11. Elfaki NK, Abdulraheem I, Abdulrahim R. Impact of e-learning vs traditional learning on student's performance and attitude. International Journal of Medical Research & Health Sciences. 2019 Dec; 8(10):76-82.

IRSTI 76.29.47: https://doi.org/10.26577/IAM.2022.v3.i2.05

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MORTALITY AND MORBIDITY RATE DUE TO SEVERE PNEUMONIA IN CHILDREN 2-59 MONTHS FOR ONE YEAR IN MIRWAIS REGIONAL HOSPITAL PEDIATRIC DEPARTMENT KANDAHAR AFGHANISTAN

Children's morbidity and mortality from respiratory disorders continue to be a serious problem, particularly for children under the age of five. Conduct research on demographic and clinical aspectsand prognosis of severe pneumonia in children aged 2 months to 5 years who were hospitalized to the pediatric unit of the Mirwais Regional Hospital in Kandahar, Afghanistan.

In the pediatric ward of the Mirwais Regional Hospital in Kandahar, Afghanistan, a cross-sectional research was conducted. Information was gathered, compiled, and analyzed from the medical records of each case at the hospital for all patients with severe pneumonia who were admitted into the pediatric ward at MRH in the period between November 10, 2018 and November 9, 2019. The patients' ages ranged from 2 months to 5 years. The data was then analyzed using SPSS version 22.0. A multivariate logistic regression model was used to identify characteristics related to pneumonia mortality.

There were 462 instances of severe pneumonia, and 256 (55.4%) of those cases were in male and 206 (44.6%) in female.

The total mortality rate was 57 (12.75) percent, while 390 patients (87.24) were successfully treated. Regarding residence, 260 (62.3%) were rural residents, while 202 (43.7%) were urban. During the winter and fall seasons, there were more cases admitted. 380 patients (82.1%) fell within the 2- to 12-month age range. Out of 462 patients, 199 (43%) were malnourished, and of them, 132 (28.57%) were severely malnourished (P-value: 0.0001 OR=4.73). According to their age, about 103 (22.2%) patients received all recommended vaccinations, 51 (11%) patients were not vaccinated, and 308 (66.5) patients received some vaccinations. 167 (36.1%) patients were fully breastfed.

Keywords: Severe pneumonia, children, Kandahar, mortality.

Introduction

Bacterial pneumonia is the greatest cause of mortality (23% of deaths) for children between the ages of 27 days and five years, according to estimates from a research on the worldwide disease burden [1]. According to estimates there are 150 million instances of pediatric pneumonia each year, 95% of which occur in underdeveloped countries [2]. Compared to industrialized countries, where the rate is just 4.3%, pneumonia kills 20% more children under five each year in underdeveloped countries [3]. In 2013, 0.9 million children died from pneumonia, and more than 95% of the fatalities occurred in low- and middle-income countries [4]. Pneumonia, one of the most dangerous and difficult conditions were the three categories into which the WHO previously separated CAP.

Only rapid breathing was classified as pneumonia, rapid breathing and tightening of the chest as severe pneumonia, and rapid breathing and tightening of the chest combined with any of the danger signs like difficulty swallowing, drowsiness or altered level of consciousness, convulsion, or cyanosis was classified as extremely serious illness. In order to distinguish between mild pneumonia and severe pneumonia, WHO [2014] CAP in children under the age of five was recently separated into two groups. Rapid breathing with or without chest in-drawing is now classed as pneumonia, and fast breathing with any of the warning signs is classified as severe pneumonia.

Material and Methods

This study, which was conducted on children aged 2 months to 5 years who had severe pneumonia at the pediatric department of Mirwais Regional Hospital in Kandahar, Afghanistan, in the period between November 10, 2018 – November 9, 2019, was hospital-based, prospective, and record-based. Children who had a clinical diagnosis of severe pneumonia were included in the trial, regardless of their gender or ethnicity. The WHO 2014 criteria for serious pneumonia served as the foundation for the solely clinical diagnosis of the condition.

MRH is a governmental referral hospital for children which is also supported by ICRC. The hospital treats patients who are referred from other Afghan provinces as well as residents of Kandahar and the surrounding area. The medications, the ward fees, and the consultation are all free. The hospital contains 600 beds throughout its several departments.

Data were collected and entered into already prepared questioners prior to the start of the study with approval from the child's mother or a close relative verbally providing consent, the hospital's chairman, and the ethics committee. All children with a clinical diagnosis of severe pneumonia between the ages of 2 months and 5 years were included in the study. From the medical records, specifics on the patient's demographics, socioeconomic status, test results, breastfeeding, nutritional status, and problems were gathered and placed into a questionnaire before being analyzed.

Statistical analysis: The percentages for the various parameters under study were obtained using SPSS version 22.0 for the statistical analysis.

To identify variables associated with pneumonia mortality, a multivariate logistic regression model was utilized.

Inclusion criteria: Patients from two months to five years old with serious pneumonia.

According to WHO guidelines the diagnosis of severe and very severe pneumonia was made. [5].

Exclusion criteria: Children below two-months of age and above five-years old, with CHD, asthma, thalassemia and other syndrome anomalies presenting as pneumonia, were excluded.

Results

462 kids in all were treated throughout the research period, which ran from November 10, 2018 to November 9, 2019 according to the demographic profile. 206 women and 256 men.

Their mean age was 9.227±7.75SD, from 2 months to 59 months. It indicates the population's demographic characteristics under study. Age was five months on average (range 2-59 months). Male patients made up 256 of the patients, or 55.4%. In the first quarter we see an increase in the number of cases hospitalized. First quarter (January, February and March) and also quarter 4 (October, November and December). 380 (82.1%) patients were in the age group of 2- 12 month. Ut of 462 patients (43%) included in the study were malnourished out of malnourished children 132(28.57%) had severe malnutrition P-value (0.0001 OR=4.73). About 103 (22.2%) patients were completely immunized according to their age, 51(11%) didn't take any vaccination and the remaining 308(66.5) were partially vaccinated. 167 (36.1%) patients were exclusively breastfed. Factors associated with mortality of children presented with severe pneumonia are tested through running multivariate logistic regression model for 447 observations after excluding 15 who left the hospital before observing the outcome (cure or death). 390 children (84%) have cured and successfully discharged from Mirwais Regional Hospital, 57 children (12.75%) have died while 15 children (3%) have left the hospital against medical advice. Male to female ratio (61.4:38.59%). 177 (38.3%) children had history of exposure to smoking. Table1 shows factors associated with pneumonia mortality clinical feature which were differently statistically significant in severe pneumonia children. Mortality was higher among the patients who had DLH (Days live in hospital) hospital less than 72 hours of onset of illness (p=0.0001).it mean those were in hospital for ≤3days died soon. Also, children with cyanosis, convulsion, no conscious, fever, (p value=0.0001) wheezing (p value = 0.014), those who need for O2 (p value =0.03) died more than who doesn't need for oxygen, 288(62.3%) X-ray not done and for remain 174(37.7%) x-ray was done for them (Table2).

Table 1 – Descriptive Statistics. Of severe pneumonia children

Descriptive Statistics						95% CI	
Characteristic	N	Minimum	Maximum	Mean	Std. Deviation		
Age	462	2	54	9.22	7.775	8.46	9.96
Weight per kg	462	2	18	6.11	2.074	5.92	6.30
Height per cm	462	48	102	65.59	8.358	64.76	66.34
Fever	462	35	42	37.79	.837	37.71	37.86
Duration of breast feeding in months	462	0	24	4.45	4.973	3.99	4.94
Number of smokers at home	462	0	4	.52	.784	.44	.59
Heart Rate per minute	462	108	250	147.71	17.755	145.98	149.24
DLH	461	1	19	5.74	3.205	5.49	6.07
Respiratory Rate per minute	462	50	104	68.16	8.968	67.24	68.96

Table 2 – Tofu his table show Factors associated with severe pneumonia mortality

Multivariate Logistic Regression Model for factors associated with pneumonia mortality								
	B	S.E.	Wald	Df	P-value	Odd Ratio (OR)	95% C.I. for OR Lower	Upper
Cyanosis	1.604	560	8.195	1	004	4.974	1.7	14.9
Consciousness	1.944	591	10.815	1	001	6.988	2.2	22.3
Refuse to feed	1.723	660	6.821	1	009	5.604	1.5	20.4
X-rays done	-1.858	650	8.179	1	004	156	0.04	0.6
Admission days			45.250	2	000			
4-7 days	-3.622	591	37.514	1	000	.027	0.02	0.09
≥7 days	-6.200	1.160	28.573	1	000	.002	0.000	0.020
Mother age			9.841	2	007			
30-40 years	-1.203	1.119	1.156	1	282	300	0.03	2.7
>40 Years	614	1.099	312	1	577	1.847	0.2	15.9
Antibiotics given at hospital			21.166	7	004			

Discussion

Among our analysis, 380 incidences of severe pneumonia, or 82.4% of all cases, were recorded in children between the ages of two and twelve months. Which has same result with the done in rural western In Nepal, pneumonia was also more common in infants under one-year old than in children aged one to five [6]. In our study, the male to female ratio was 1.24:1.

Similar findings in a comparable study in Karnataka, India, found that 62.6% of the participants were men and 37.4% were women (ratio 1.67:1). In the under-five age group, more male patients were hospitalized for treatment of pneumonia. This may be the result of our society's preference for treating male children [7]. During the first quarter, more cases were admitted. (months of January, February and March) and also quarter 4 (October, November and December). In winter and fall which rainy and dry season respectively. Which is same result with According to WHO data from 2008, pneumonia cases in tropical climates peaked during the rainy season. According to seasonal distribution, our analysis showed a similar trend [8]. in the present study Out of 462 patient the patients 199 (43%) included in the study had malnutrition out of malnutrition children 132(28.57%) had severe malnutrition. and a study from Kolkata found a similar conclusion: malnutrition was substantially linked to the development of acute respiratory infections (ARI) in children under five [9]. In our study, about 103 (22.2%) patients were completely immunized regarding to their age, 51(11%) didn't take any vaccination and the remaining 308(66.5) were partially vaccinated This discrepancy could be caused by issues with several aspects of vaccination coverage in our study area (as per the NIS nation immunization schedule), as well as parental ignorance and pessimism. In our study, 167 (36.1%) patients were exclusively breastfed, this low rate of exclusive breastfeeding in our analyzed cases may be the result of mothers' lack of knowledge of the advantages of exclusive breastfeeding. Among survivors, the average hospital stay was 5.74±3 days. 3 days for those who did not survive. In a study from Karnataka, it was shown that the group with the most severe pneumonia required a longer hospital stay. Very severe pneumonia group children in our study had shorter hospital stays because more early fatalities occurred as a result of the illness's more serious character. [9]. In our investigation, severe pneumonia was the primary cause of 57 (12.75%) deaths overall. 9 (6.38%) from severe pneumonia and 22 (15.6%) deaths were recorded in cases of very severe pneumonia. In a 2017 study by Kumar AMK et al, it was shown that 3% of children with acute lower respiratory tract infections who were between the ages of 2 months and 5 years old died. In contrast to their research group, there may have been more cases of very severe pneumonia in our study, which may have contributed to the study's higher mortality rate. Another contributing factor can be the severity of the sickness and the delay in getting to the referral hospital (Mirwais Regional Hospital

Conclusions

Severe pneumonia was more likely to occur in infants than in adults.

Children with severe pneumonia made up the bulk of patients who died when they were admitted to the hospital more than 72 hours after the onset of their illness. Children continue to carry a significant burden for respiratory infections. If we wish to reduce the population's morbidity rate, we should pay special attention to children's respiratory diseases. It is necessary to undertake a detailed analysis of the epidemiological variables associated with morbidity

and mortality in the community in order to determine the prevalence of the illnesses and plan measures for treating them.

*Limitation.*It does not accurately reflect the prevalence of severe pneumonia in the general population in all of its forms and etiologies because it was a hospital-based study.

*Acknowledgements.*We are thankful to associate clinical professor M.A. Shifa and Dr. M.Sadiq (MD, DCH) chief of pediatric department for his valuable inputs. We also like to thank the staff of the Medical Records Department of pediatric Mirwais Regional Hospital, Kandahar.

References

1. Liu L, Oza S, Hogan D, Perin J, Rudan I, Lawn JE, et al. Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis. Lancet. 2015;385(9966):430–40.

2. Rohit C Agrawal. Pneumonia. A Parthasarathy. IAP Text book of Pediatrics. 5th ed. Jaypee Brothers Medical Publishers (P) Ltd. 2013;8.6:470-74

3. Black RE, Cousens S, Johnson HL, Lawn JE, Rudan I, Bassani DG et al. Global, regional, and national causes of child mortality in 2008: a systematic analysis. The Lancet. 2010 Jun 5; 375(9730):1969-87

4. Fischer Walker CL, Rudan I, Liu L, et al. Global burden of childhood pneumonia and diarrhoea. Lancet2013; 381:1405–16.

5. Rudan I, Boschi-Pinto C, Biloglav Z, Mulholland K, Campbell H. Epidemiology and aetiology of childhood pneumonia. Bull World Health Organ. 2008;86(5):408-416.

6. Banstola A, Banstola A. The Epidemiology of Hospitalization for Pneumonia in Children under Five in the Rural Western Region of Nepal: A Descriptive Study. PLoS ONE. 2013 August;8(8): e71311.

7. Divyarani DC, Goudappa R Patil, K Ramesh. Profile on risk factors of pneumonia among Under-five age group at a Tertiary care hospital, International Journal of Current Microbiology and Applied Sciences. 2014;3(6):750-54.

8. Rudan I, Boschi-Pinto C, Biloglav Z, Mulholland K, Campbell H. Epidemiology and aetiology of childhood pneumonia. Bull World Health Organ. 2008;86(5):408-416.

9. Kumar AMK, Badakali AV, Mirji G, Vanaki RN, Pol R. Clinical profile and outcome of acute lower respiratory tract infection in children aged between 2 months to 5 years. International Journal of Contemporary Pediatrics. 2017;4(1):105-09.

CLINICAL CASES

IRSTI 76.29.51: https://doi.org/10.26577/IAM.2022.v3.i2.06

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TOXOPLASMOSIS OF THE CENTRAL NERVOUS SYSTEM IN HIV PATIENTS

Currently HIV infection in Kazakhstan is mainly spread among population groups with risk taking behavior (injection drug users – IDUs, sex workers – SWs). The lesions and fatalities in patients with HIV infection are mainly caused by complications, i.e. the development of opportunistic infections and secondary diseases. Timely diagnosis of these conditions determines the success of treatment and life expectancy of patients. Among superinfections the following ones take the lead: mycoses (pneumocystosis, candidiasis, cryptococcosis, coccidioidosis), diseases caused by a group of herpes viruses (herpes simplex, herpes zoster, cytomegalovirus infection, Epstein-Barr virus infection, Kaposi's sarcoma), bacterial infection (tuberculosis, atypical mycobacteriosis, salmonellosis), protozoosis (toxoplasmosis, cryptosporidiosis). Multi-infections are common as well. Opportunistic infections are insidious in humans and take the form of endogenous infections; they as well are activated with the development of clinical manifestations along with formation of immunodeficiency and, accordingly, cause severe and even fatal diseases.

Keywords: HIV infection, opportunistic infections, secondary diseases, toxoplasmosis.

Introduction

Infection rate of the population with toxoplasmosis in different countries of the world varies between 6 and 90% of the population. In various countries of the world the infection mostly hits the areas where it is customary to eat undercooked meat. It is hard to determine the morbidity rate since there is no mandatory registration of patients with toxoplasmosis. The rural population is infected more than the urban population due to the large number of cats [1]. According to A. P. Kazantsev, the infection rate of men is less than 1% of those observed, while among women it makes up 3-5% of those surveyed.

Opportunistic infections are insidious in humans and take the form of endogenous infections; they as well are activated with the development of clinical manifestations along with formation of immunodeficiency and, accordingly, cause severe and even fatal diseases [2].

Within secondary diseases in HIV patients, toxoplasmosis ranks third, along with pneumocystis pneumonia, and follows tuberculosis and CMV infection, and accounts for 7.4%. There is an increase in the number of patients in the late stages of HIV infection who develop opportunistic, secondary infections. Toxoplasmosis is the most important opportunistic infection of the central nervous system (CNS) in HIV patients. It accounts for 50-70% of all parasitic diseases in AIDS and it ranks third among fatal outcome in patients at the late stage of HIV infection. Almost all cases of toxoplasmosis in HIV patients are associated with reactivation of a latent infection [3].

According to A.B.Peregudova central toxoplasmosis is the most common cause of CNS pathology, making up 32%. Other secondary lesions of the CNS were recorded less frequently: tuberculous meningoencephalitis – 22.4%, fungal encephalitis – 6%, secondary purulent meningitis – 7.6%, malignant tumors of the CNS – 3.7%, CMV encephalitis – 1.6% and others.

In the Republic of Belarus, Gomel region within opportunistic diseases, neuroAIDS (29.1%) ranks second after tuberculosis. In the etiological structure of neuro AIDS, toxoplasmosis of the brain prevails (32%) and mortality is 19.5% [4-5].

Materials. Case Report

M., born in 1986, delivered to the emergency department of the regional hospital in Taraz by an ambulance team (EMS) in an unconscious state, not reacting to painful stimuli.

The patient's history was taken from his father: the son came to Taraz to undergo alternative therapy and on May 31, 2019 he got an electric shock session. On therapy epileptic seizures occurred with loss of consciousness and tonoclonic spasms every 5 minutes. In total 3-4 epileptic seizure clusters were recorded. An ambulance team was called, which delivered the patient to the intensive care unit (ICU) due to ongoing seizures.

From the recorded medical history of the patient. Between 08.04 and 16.04.2019 he underwent

medical examination and took treatment at the regional hospital in Almaty. According to the patient the first focal convulsive seizures occurred in April 2019. MRI examination of his brain on 04/09/2019 showed the following: a pattern of unspecified mass in the right hemisphere; taking into account the ring-shaped accumulation of a contrast agent, it is required to differentiate between a parasitic lesion and an oncological disease. He visited a neurosurgeon and an oncologist. Received symptomatic therapy. He then was discharged from the hospital with the following diagnosis: Residual encephalopathy. Space-occupying mass in the right parietal region. Hypertensive syndrome. Convulsive syndrome. Condition after an epileptic seizure. It was recommended to have an MRI with contrast 2 months later. Starting from 20.05.2019 he had been experiencing weakness in the left arm and leg, had had difficulty walking.

From his life history: he grew and developed according to age. According to his father, he had no viral hepatitis, tuberculosis nor venereal diseases. No blood transfusions. He had no closed craniocerebral injuries. No history of allergies. Works as a choreographer.

Objective condition at admission: general condition is severe due to cerebral insufficiency. Satisfactory nutrition. Normostenik. The skin and visible mucous membranes are of normal color, clean. Peripheral lymph nodes are not enlarged. The musculoskeletal system is unremarkable. Body temperature is 36.6°C. The chest is of the usual form, both halves are equally involved in breathing. By percussion: percussion sound in all lung cavities. By auscultation: vesicular respiration, no wheezing sounds. RR is 18 per minute. There is no pathological pulsation of large vessels. Cardiac borders: the right border is along the right edge of the sternum, upper border is in the 3rd intercostal space, left border is 1.0 cm outward from the mid-clavicular line. Heart sounds are muffled, the rhythm is correct. BP is 130/80 mm Hg. Heart rate – 98 beats / min. No swallowing problems. The tongue does not stick out. The abdomen is not swollen, soft on palpation. The liver and spleen are not palpable. No stool for 2 days. Kidney punch is negative on both sides. Urination through a catheter. No peripheral edema. CNS: level of consciousness according to the Glasgow scale is 8b, coma – 1. He does not respond when addressed. Weak response to painful stimuli. Rigidity of the occipital muscles is 1.5 – 2 p / p. Skull brain nerves: palpebral fissures D=S, pupils are uniform, no anisocoria, photoreaction is preserved, quick. Weakness of convergence from both sides. Trismus of masticatory muscles, pharyngeal reflexes and a reflex from the soft palate are evoked. Tendon reflexes – D > C. Sensitivity and muscle strength are not differentiated. Tonic convulsions are observed in left arm and left leg. Pathological foot signs: Babinski's sign (+) on the left. There are no meningeal signs.

MRI of the brain (06/01/2019): MRI signs of the mass in the parietal lobe on the right and the frontal lobe on the left with multiple foci. Differentiate between a parasitic lesion of the brain (toxoplasmosis) and NEO. An MRI of the brain with contrast is recommended.

Ultrasound of the abdominal cavity organs (06/03/2019): Diffuse changes in the liver and pancreas. Chronic cholecystitis. Bilateral pyelonephritis, Uratic diathesis. ECG (06/01/2019): left atrial hypertrophy. Syndrome of early repolarization of the ventricles. T-wave inversion in the septal region.

X-ray of the chest (06/05/2019): no focal and infiltrative shadows on the lung cavities were detected on the plain chest radiograph in the direct projection. The lung pattern is deformed. The roots are structural, compacted. Sinuses are free. The heart is not enlarged. Indirect signs of chronic bronchitis.

Ophthalmologist's comments (06/01/2019): background retinopathy of OU.

Neurosurgeon's comments (06/01/2019): Status epilepticus. Condition after serial convulsive seizures. Todd's post-seizure paralysis on the left. Competing disease: metastasis of the brain? To clarify the diagnosis upon MRI of the brain with contrast.

MRI of the brain with contrast (06/02/2019): MRI signs of a parasitic brain lesion, most likely acute necrotizing toxoplasmic encephalitis. Cerebral edema.

Consultation of an infectious disease specialist (06/03/2019): CNS toxoplasmosis? HIV infection? EIA blood test for HIV, toxoplasmosis, echinococcosis. Spinal puncture after stabilization.

Repeated consultation of an infectious disease specialist (06/06/2019): chronic toxoplasmosis of the central nervous system. Meningoencephalitis, severe. Cerebral edema. Coma 2. B-20. Consultation of an infectious disease specialist of the regional AIDS center: HIV – infection, 4th clinical stage. Toxoplasmosis of the brain. Blood samples were taken for CD4 lymphocytes, viral load, and AIDS-defining diseases. ART was prescribed according to the scheme.

Table 1 – The results of a general blood test in dynamics

Erythro-cytes, 10^12/l	Hemo-globin, g\l	platelets, 10^9/l	Leuko-cytes 10^9/l	Eosino phyla %	Bazo phyla %	Banded neutrophils[1], %	Segmen-tonuclear neutrophils[2] %	Lympho-cytes, %	Monocytes, %	ESR, mm/h
4.75	146	299	5.420	1	0	10	50	27	12	18
5.16	158	248	9.980	0	0	15	58	18	9	22
5.06	156	236	12.200	0	0	22	68	5	5	22
4.0	122	171	3.290	3	0	10	51	21	15	22
4.28	131	219	6.820	2	0	19	57	15	7	20
4.09	125	249	7.320	2	0	20	51	18	9	22
4.13	127	290	10.970	2	0	26	59	6	7	22

In the general blood test the indicators of red blood (table 1) and the number of platelets stayed within the reference values. The number of blood leukocytes varied from leukopenia (3.290 x10^9/l) to leukocytosis (12.220 x10^9/l), but more often normocytosis prevailed. The number of neutrophils: in 2 cases there was neutrophilia, but a stab shift of the formula to the left was a constant sign of a bacterial infection. The absolute number of lymphocytes ranged from 1796 cells/ml of blood to 611 cells/ml of blood. The number of blood monocytes and accelerated ESR were reduced to permanent numbers. The results obtained indicated the bacterial etiology of the infectious process, without damage to the bone marrow (erythrocyte and platelet sprouts).

In the general analysis of urine, there were observed a large number of leukocytes, erythrocytes 1-2 per HPF, bacteria and mucus. Biochemical liver tests in dynamics show no irregulrarities (table 2).

Table 2 – The results of biochemical tests of the liver in dynamics

ALT MU/ml	AST MU/ml	Total bilirubin mmol/l	Sugar mmol/l	Total protein g/l	Na mmol/l	Creatinine µmol/l
21	36.6	9.1	7.1	75.2	145.6	92
-	-	-	5.6	55.6	139.9	-
-	-	-	-	56.6	137.5	-

EIA for antibodies of class IgM, IgG for echinococcosis, toxoplasmosis showed negative results. EIA for viral hepatitis B (HBsAg) and viral hepatitis C (anti HCVAT) is negative.

From the first day in hospital, taking into account the primary results of the examination, the following drugs were prescribed: rovamycin (9 million/day), CEF-3 (2.0 g/s), metrogil (300 mg/day) and pathogenetic and symptomatic therapy.

LFIA for antibodies to HIV proved positive. Immunoblot for HIV – (+), titer 15.4. Additionally, tests for CD4-lymphocytes and viral load were taken.

The results of the immunogram: CD4 – 18 cells; CD3 are -480 cells/µl; CD8 are -445 cells/µl. The CD4/CD8 ratio is 0.04. VL is 469449 copies / ml / log 10 – 5.67.

Based on the results of an additional examination, the following diagnosis was established: HIV infection, 4th clinical stage. Toxoplasmosis of the brain. ART prescribed: AZT/ZTS+DTG. And cotrimoxazole was prescribed as well.

At the insistence of the parents, the patient was discharged for home treatment after 12 days of treatment in the hospital and died 5 days later.

In the described case during the initial visit of the patient in April 2019 in a hospital setting he was not tested for HIV, although the young man was subject to examination for this disease since he had had focal epileptic seizures since April 2019 at normal body temperature and showed no symptoms of meningoencephalitis upon detection of ring-shaped accumulations of a substance in the right hemisphere on the brain MRI. This indicates that doctor do not raise flags as related to HIV infection and late diagnosis and treatment of the disease. The lack of specific treatment leads to the steady progression of the disease, the addition of opportunistic diseases and increased mortality.

The patient's MRI examination revealed multiple lesions in the frontal and parietal regions of the right hemisphere. According to Ermak T.N. and Peregudova A. B. most often the foci were localized

in the frontal (70.8%) and parietal (61.1%) areas of the brain. Tumash O.L. with co-authors noted multiple foci ranging in size from 2 to 40 mm, which had rounded shape with blurry edges. In addition, the foci often intensified contrast along the periphery, according to the type of «targets», which was noted by the radiologist during the primary MRI.

The anamnesis shows that the patient's disease began with the appearance of focal seizures, which corresponded to the acute onset of the disease, which was noted in 21.3% of patients, but the clinical picture had to be differentiated from acute cerebrovascular accident, less often the disease began with tonic-clinical seizures and they were the only manifestation of the disease. During the first week of illness, 65.9% were hospitalized with an acute onset, and some were admitted after 2–6 months (2). In our case, the patient was admitted for treatment at the end of the 2nd month from the onset of the disease.

The content of CD4-lymphocytes was at a critically low level (18 cells/ml) and at the same time a high viral load was detected – 469,449 copies/ml. The same data are provided by Peregudova A.B. and Tumash O.L with co-authors. They note the results obtained in 66.2% and 52.2% of cases, respectively. The negative result of the examination for antibodies to toxoplasma must be due to a critical decrease in the number of T-helpers, the main function of which is to stimulate antibody genesis.

Conclusion

The rapid progression of HIV infection is associated with the development of secondary diseases. Practitioners should be wary of AIDS-associated diseases, which will contribute to early verification of HIV infection.

References

1. Kazantsev A.P. Toxoplasmosis. – Leningrad: «Medicine», Leningrad branch, 1985

2. Mikhailov N.R., Kalinina T.N., Tuchkov D.Yu., Losin E.I., Abakumov G.G. Toxoplasmosis of the brain in HIV patients in the city of Orenburg // J: Bulletin of the Orenburg State University. – No. 1 (176) / January 2015.

3. Peregudova A.B. Toxoplasmosis in HIV patients. Features of the clinic and diagnosis. Abstract of the dissertation for the degree of candidate of medical sciences. – M., 2013.

4. Ermak T.N., Peregudov A.B. Localization of foci in cerebral toxoplasmosis in HIV patients // Magazine: Therapeutic archive. – 11, 2014. – Pp. 24 – 28.

5. Tumash O.L., Zhavoronok S.V., Kozorez E.I. Toxoplasmosis in HIV-infected people // Magazine: Clinical infectology and parasitology. – 2017. – Pp. 239 – 241.

IRSTI 76.29.39: https://doi.org/10.26577/IAM.2022.v3.i2.07

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GALLSTONE DISEASE COMPLICATED WITH MIRIZZI SYNDROME: A CLINICAL CASE

This article represents the difficulties in diagnosing and treating the patients with gallstone disease complicated by Mirizzi syndrome and obstructive jaundice. The manifestation of the disease is characterized by many clinical, laboratory and instrumental symptoms found in acute and chronic cholecystitis. Among them, it is worth noting pain in the right subcostal region, the jaundice, increased body temperature and symptoms revealed during ultrasound. However, in some patients, the disease is asymptomatic and its first manifestation may be obstructive jaundice. Because of the presence of gallstones and jaundice, they are often confused with other obstructive conditions. Preoperative diagnosis is complex and often overlooked. The difficulties in diagnosing Mirizzi syndrome, the high risk of damage to the biliary tract, as well as the wide spectrum of surgical treatment determine the relevance of this study.

A literature review has been made on the topic with the clinical situation analyzed.

A 62-year-old patient was admitted with a diagnosis of biliary tract obstruction. The patient was diagnosed with gallstone disease. As a result, gallstone disease complicated by Mirizzi syndrome was diagnosed and surgical treatment was performed.

Keywords: choledocholithiasis, Mirizzi syndrome, biliary drainage, biliary anatomy, surgery.

Introduction

Mirizzi syndrome is a severe complication of gallstone disease characterized by compression of the proximal hepaticocholedochus, formation of a stricture, or formation of a cholecystobiliary fistula. Mirizzi syndrome occurs in 0.2-5.7% of patients suffering from gallstone disease [1].

In 1948 Argentinian scientist P. L. Mirrizi described the pathological syndrome due to obstructive jaundice in patients or the occurrence of cholecystocholedocheal fistula upon the movement of stones in the common bile duct. Currently, 2 types of Mirizzi syndrome are distinguished.

Type I – compression of the hepaticocholedochus by a concretion in the neck of the gallbladder or in the bile duct.

Type II – cholecysto-choledocheal fistula in the gallbladder and common bile duct. [2].

C. McSherry et al., A. Csendes et al. and T. Nagakawa et al. McSherry (1982) classifications were made based on endoscopic retrograde cholangiopancreatography (ERCP) data [3].

Currently the most widely used classification is based upon studies of C.K. MCSHERRY and A. CSENDES ET AL.

Mirizzi syndrome is divided into four types:

Type I – compression of the hepaticocholedochus by a concretion in the neck of the gallbladder or in the bile duct.

Type II – cholecysto-choledocheal fistula, occupying less than 1/3 of the total bile duct.

Type III – cholecysto-choledocheal fistula, occupying 2/3 of the total bile duct.

Type IV is a cholecysto-choledocheal fistula that takes the entire part of the common bile duct, accompanied by destruction of the entire wall of the hepaticocholedochus [4].

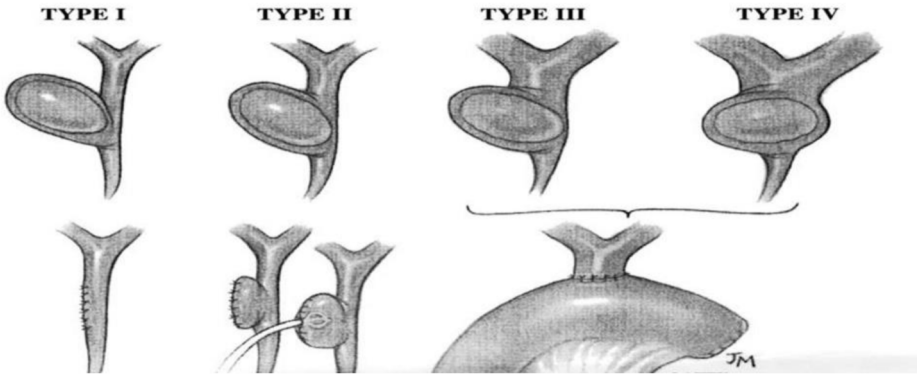

Figure 1 – Types of Mirizzi syndrome [5]

Diagnosis and treatment methods of Mirizzi syndrome are still relevant.

In the literature there are basic and additional criteria in the predictive diagnosis of Mirizzi syndrome.

Main criteria:

– emergence of the disease after many years;

– a feeling of pain for more than 1 hour or more often, its location is in the upper part of the abdomen or in all parts;

– during an physical examination – pain in the upper right part of the abdomen, jaundice;

– ultrasound signs – thickening of the wall of the gallbladder and a double image;

– detection of a wedge-shaped stone in the neck of the gallbladder;

– impossibility of visualization of the inflammatory infiltrate and neck of the gallbladder.

Additional criteria:

– complaints – belching with bitter, skin itching;

– on palpation – a feeling of pain under the right rib;

– positive symptoms of Courvoisier and Boas-Svirsky;

– in the laboratory study: ALT>130.0 IU/l, AST>116.0 IU/l, ESR>17 mm/h, hyperbilirubinemia of various degrees (depending on the type of MS), increased alkaline phosphatase level.

Clinical case

Patient K.N. At the age of 62, he was admitted to the National Scientific Surgery Center named after A. N. Syzganov with complaints of pain in the epigastric region, general weakness, yellowing of the skin, changes in the color of urine, and an increase in body temperature to 37.5 at the onset of the disease.

From the medical history: the patient has been ill for three days. That day he had a sharp pain in the epigastric region, nausea, and vomiting. At home he administered omez, ketotop with no effect. In dynamics, yellowing of the skin layer and increased general weakness were observed. On 24.05.2022 he was admitted to the regional hospital and obtained conservative treatment. On 25.05.2022 according to the multispiral computer tomography of the abdomen: a formation spread to the middle 1/3 of the choledoch, confluence, right liver core was detected, the result was cholangiocarcinoma, Klatskin's tumor III? According to laboratory research: total bilirubin is 110 mkol/l. It was not possible to make an ERCP on 26.05.2022. The patient was referred to A.N.Syzganov National Scientific Surgery Center.

Surgery history: (for many years he has been on the "D" report of the cardiologist due to heart rhythm disorders at his place of residence; he takes 2.5 mg of bisoprolol once a day). In 2013-2014 he had 3 courses of radiofrequency catheter ablation due to heart rhythm disorders.

Physical examination: the general condition of the patient is moderate. His mind is lucid. Skin surface, visible mucous membranes are clean. Peripheral lymph nodes are not enlarged. The tongue is wet, covered with white fur, the pharynx is not hyperemic. In the lungs: breathing is vesicular, no wheezing. Heart tones are slowed down, the rhythm is correct. AD – 110/70 mm Hg, heart beat rate -83/ 1 min, respiratory rate -18/ 1 min. The percussion test is negative on both sides. Urination is without obstructions, painless, 800 ml per day. Abdomen is symmetrical, soft during palpation, painful under the right rib and in the epigastric area. The liver is at the edge of the rib cage.

The results of the analysis at the time of the patient's admission.

Full blood analysis: Hemoglobin = 127.0 g/l; erythrocyte = 4.56 10^12/l; Hematocrit = 38.60%; platelets = 90.0 10^9 / l; leukocytes = 30.00 10^9/l;

segment kernel (%) = 97.2 %; monocytes (%) = 0.9%; Lymphocytes = 1.9%;

Full urine analysis: leukocytes – 5.00 / µl, relative density 1025, reaction – acid, number of erythrocytes – 15.00 ery/µl.

Biochemical blood analysis: ALT = 94.80 units/l; AST=41.60 units/l; bilirubin (total) = 103.00 µmol/l; bilirubin (direct) = 101.70 µmol/l; glucose = 5.93 mmol/l; ionized calcium = 1.07 mmol/L; potassium = 3.6 mmol/l; creatinine = 266.00 µmol/l; urea = 20.10 mmol/l; sodium = 135 mmol/l; total amylase = 91.0 u/l; total protein = 54.0 g/l; albumin = 33.3 mg/l; C-reactive protein = >374.01 mg/l;

Coagulogram: prothrombin time (sec) = 13.7 sec.; Prothrombin index = 70.60 %; MNO = 1.20; thrombin time = 13.8 sec.; APTV=27.90 sec.; Fibrinogen = 8.17 g/l;

Determination of blood gases and electrolytes with additional tests (lactate, glucose, carboxyhemoglobin) in the analyzer: cHCO3 – (P, st), c = 20.00 mmol/l; FIO2 = 21000; 2 = 47 mm Hg; CO2 = 32.8 mm Hg. pH = 7.379; tab = 11.6 g/l; 2 = 77.0%; Na+ = 136 mmol/l; Cl – = 106 nmol/l; Ca++ = 0.65 mmol/l; k+ = 2.7 mmol/l; Glucose = 5.7 mmol/l; Lactate = 1.5 mmol/l; co2,c = 12.30 rev% ; p50, c = 30.5 mm Hg, cbase (Ecf),c = -5,300 mmol/l; PCO2(t), c = 32.8 mm Hg; Htc(c) = 35.8%; FO2Hb = 75.3%; FCOHb = 1.3%; FMetHb = 0.9 %; Hb = 22.5%; Bilirubin = 80.00 µmol/l; pH(T),c = 7.38%; pO2(T),c = 47.10 mm Hg;

Determination of alpha-fetoprotein (AFP) in blood serum by EIA method: AFP= 0.53 IU/ml; (n=0-5.8 IU/ml).

Detection of tumor antigen (CA 19-9) in blood serum by EIA method (27.05.2022): CA 19-9 = 539.5 U/ml; (n=0-34 IU/ml).

EIA for hepatitis B, C: negative.

Figure 2 MRI of the abdominal cavity: signs of choledocholithiasis, cholangioectasia. Virsungectasia.Abdominal ultrasound: echo image of biliary hypertension with distal blockage in the confluence. Gallbladder function is not determined. Choledoch walls are thickened, the image may correspond to Klatskin's tumor. A formation with dimensions of 3.4*3.5*3.6 was detected in the left part of the liver. In the distal region of the choledochus, the walls are unevenly thickened, cavities are not defined.

Electrocardiogram: description of pathological waves heart beat rate – 130; conclusion-levocardiogram. Sinus tachycardia. Shortening of the PQ interval. Left ventricular hypertrophy. Diffuse myocardial changes.

X-ray results: No new focal shadows were detected. C-shaped scoliosis in the thoracic spine.

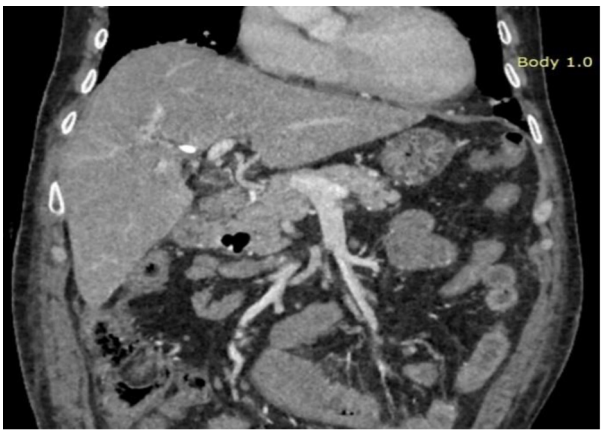

Figure 2 – MRI of the abdominal cavity: signs of choledocholithiasis, cholangioectasia. Virsungectasia

Magnetic resonance cholangiopancreatography (MRCP): a formation in the lower 1/3 of the choledochus that has spread to the right duct (Klatskin tumor, type III A). Intrahepatic biliary hypertension. MR-signs of diffuse compaction of the liver parenchyma, cystic formation of the left part. Chronic cholecystitis. Diffuse pancreatic changes (chronic atrophic pancreatitis). Chronic bilateral pyelonephritis with simple cysts according to Bosniak I in both kidneys. Intrahepatic bile ducts are visualized, expanded (partial and segmental). The confluence of bile ducts is deformed by the type of bifurcation. The right lobe is up to 1.0 cm, the left one is up to 1.2 cm. Confluence block appears due to the intrahepatic biliary duct and the common hepatic duct extending into the intrahepatic right lobular duct. A round 1.1 cm diameter concretion is visualized in the middle 1/3 of the choledoch. The size of the gall bladder is 3.8*1.2 cm, the amount of bile is small, the wall is uniform, unchanged. The follicular core is not visualized. The

lower 1/3 of the choledoch is deformed, 0.3 cm in the intrapancreatic part. The length of choledoch from bifurcation to the Faterov papilla is 9 cm.

Figure 3 Fistulocholangiography: partial liver ducts are contrasted. At the level of the terminal part of the choledochus, the shadow of the concretion is determined**.**

After the patient had been fully prepared for the surgery he was diagnosed with Obstruction of bile ducts. Klatskin tumor? Obstructive jaundice.

On May 27, 2022 a percutaneous-hepatic cholangiostomy was performed at the A.N. Syzganov National Hospital. 1000 ml of bile was secreted per day through percutaneous cholangiostomy drainage. In dynamics, total bilirubin decreased from 103 μmol/l to 87.10 μmol/l.

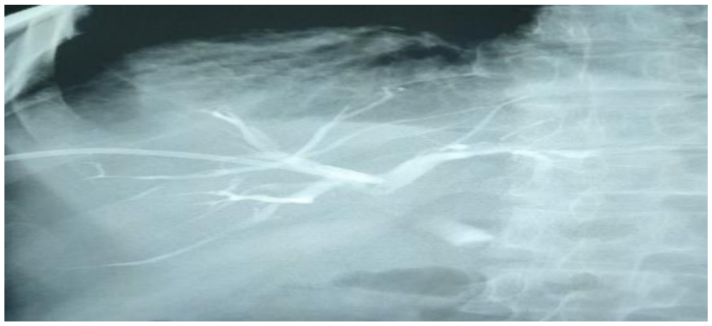

Figure 3 – Fistulocholangiography: partial liver ducts are contrasted. At the level of the terminal part of the choledochus, the shadow of the concretion is determined

After decompression of the bile ducts, until the bilirubin level returned to normal, it was decided that he be discharged to outpatient treatment.

Release status

The general condition is satisfactory. His mind is lucid. The skin, yellow mucous membranes are clean. Peripheral lymph nodes were not enlarged. No visible swelling. The tongue is wet, covered with white fur, the pharynx is not hyperemic. In the lungs: breathing is vesicular, no wheezing sound. Heart tones are silent, rhythm is normal. ABP – 110/75 mm Hg. Heart beat rate is 78 / 1 min, respiratory rate is 17/ 1 min. Abdomen is of the correct shape, symmetrical, soft during palpation, moderate pain in the right hypochondrium, epigastrium. The liver is at the edge of the rib cage. The percussion symptom is negative on both sides. Urination is unobstructive, painless. 1000 ml of bile was drained by percutaneous-hepatic cholangiostomy.

Due to obstructive jaundice and coagulopathy, the patient's treatment was corrected (bilirubin decreased to 23 μmol/l), the patient was admitted to the center for radical surgery on 28.06.2022.

Preoperative diagnosis: Klatskin's tumor?, choledocholithiasis? Obstructive jaundice. Additional diagnosis: CHD. Angina pectoris Grade II. Arterial hypertension 2 degree. CHF.

Surgery – Laparotomy. Adhesiolysis, cholecystectomy, choledochotomy, cito biopsy. Hepaticocholedochus resection, hepaticojejunoanastomy with Rou's loop, drainage of the small pelvic cavity and the iliac cavity.

During the surgery examination a clear adhesive process was detected in the abdominal cavity. The size of the liver is not increased, liquid discharge is revealed in the projection of the left part. Choledochus is 1.0 cm. A cholecystectomy was performed on the neck, with choledochal mobilization from the surrounding tissues, a total resection of the liver core was performed. Due to the identification of a suspected sealing area on the back wall of the choledochus it was decided to do a cito!biopsy. Pathological conclusion: the morphological appearance is characteristic of chronic cholecystitis. Lymph node tissue is characteristic of reactive follicular hyperplasia. Choledochus was opened from the level below confluence, a 1.1 cm concretion was removed from the middle 1/3 of the choledochus, and the right and left lobes were examined. 30 cm from Treitz's ligament to the small intestine was cut, the ileum was mobilized, an "end-to-side" small intestine-small intestine anastomosis was placed 80 cm via the Ru-ligament. Hepaticojejunoanastomy was performed by a continuous suture along the Ru ligament with an atraumatic PDS 5.0 suture. From the right side (under the anastomosis) and into the lower pelvis, a drainage tube was placed through a contraperture incision, layered sutures were placed, and an aseptic bandage was applied.

Postoperative diagnosis: Gallstone disease. Chronic calculous cholecystitis. Choledocholithia-

sis. Mirizzi syndrome type II. Additional diagnosis: CHD. Angina pectoris Grade II. Arterial hypertension 2 degree. CHF.

In the postoperative period, antibacterial, detoxification, symptomatic treatment was carried out. After normalization of the function of all organs and systems he was transferred from the intensive care unit to the surgical department. In the first days after the surgery 800-900 ml of bile was secreted by percutaneous-hepatic cholangiostomy. Subsequently, the percutaneous-hepatic cholangiostomy was lifted on the seventh day after bowel function had returned to normal.

Tests at discharge:

Common blood test: Hemoglobin = 94.0 g/l; Erythrocytes = 3.59 10^12/l; Hematocrit = 30.80 %; Average volume of erythrocytes = 85.8 fl; average amount of hemoglobin in erythrocytes = 26.2 pg; Average concentration of hemoglobin in erythrocytes = 305 g/dL; Average volume of erythrocytes (CV) = 138.0 %; Platelets = 419.0 10^9/l; Distribution of platelets by volume (Anisocytosis of thrombocytes) = 10.3 fl; average volume of platelets = 8.9 fl; Leukocytes = 6.90 10^9/l; Segment nuclear (%) = 66.0 %; Segment nuclear (abs. number) = 4.80 10^9/l; Eosinophils = 1.9 10^9/l; Monocytes (%) = 7.6 %; Monocytes (abs. number) = 0.50 10^9/l; Lymphocytes = 23.5%; Lymphocytes (abs. number) = 1.60 10^9/l; Rod-shaped = 1 %;

Biochemical blood analysis: ALT = 53.70 units/l; AST = 38.00 U/l; Bilirubin (total) = 8.00 μmol/L; Bilirubin (direct) = 6.20 μmol/l; Glucose = 4.82 mmol/l; Ionized calcium = 1.21 mmol/l; Potassium = 3.4 mmol/l; Creatinine = 48.00 μmol/l; Urea = 2.30 mmol/l; Sodium = 136 mmol/l; Total amylase = 46.0 U/l; Total sugar = 48.1 g/l;

Due to the improvement of the general condition of the patient, based on the results of the last examination, on 20.07.2022, the patient was discharged home with treatment recommendations and a drainage tube.

After 3 months, the patient underwent a comprehensive check-up at A.N.Syzganov National Medical Center, his condition was satisfactory.

Results and Conclusions

The presented clinical case and literature review resulted in the following conclusions:

1. It is necessary to carry out a complete set of diagnostic measures for early diagnosis of possible rare cases and complications during the examination and treatment of patients with acute surgical diseases of the hepatopancreatoduodenal organs;

2. Diagnosis of Mirizzi syndrome is complex and requires additional examinations;

3. Consideration of basic and additional criteria for preliminary diagnosis of Mirizzi syndrome (clinical, instrumental and laboratory);

4. One can suspect Mirizzi syndrome by paying attention to the presence of several signs in the ultrasound examination of the abdomen in patients with gallstone disease:

*”мыжылған” (сморщенный) кейіптегі өт қабы мен бауырдың оң бөліктік өт өзегінің кеңеюі;

* Enlargement of the intrahepatic bile ducts, mostly in the right part of the liver, with the location of a large concretion located in the Hartmann’s pouch close to the hepatocholedochus;

* inflammatory infiltrate in the area of the gall bladder neck and the possibility of its detection (good visualization) is low.

5. When Mirizzi syndrome is suspected, it is mandatory to perform MRCP.

6. During obstructive jaundice, a 2-stage surgery is performed. Stage 1 – drainage and decompression of the bile ducts, stage 2 – radical surgery.

Diagnosing Mirizzi syndrome in the preoperative period is very difficult for surgeons and ultrasound doctors. Its solution is the selection of adequate treatment-diagnostic tactics and prevention of complications like obstructive jaundice, calculous cholecystitis or biliary stricture disorders during surgeries for choledocholithiasis.

References

1. Revyaki V.I. Diagnosis and treatment of Mirizzi syndrome. Book: 50 lectures on surgery. Edited by V.S. Savelyeva. – M.: Media Medica, 2003.

2. Guide to biliary tract surgery / Edited by E.I. Galperina, P.S. Vetsheva. – M.: VIDAR-M, 2006. – P. 97.

3. Akhaladze G.G., Kotovsky A.E., Unguryanu T.V. etc. Mirizzi’s syndrome is a cause of iatrogenic damage of hepatic choledocho // Consilium Medicum. – 2008; 10 (8): 106–8.

4. Sanchin U., Sergelen O. Evaluation of criteria for preliminary diagnosis of Mirizzi syndrome // Bulletin of the East Siberian Scientific Center, RAMN. – 2008; 4: 137–8.

5. Clinico-pathomorphological classification of mirizzi syndrome. Zh.O. Belekov, K.S. Ismayilov, N.A. Mamanov. National Hospital of the Ministry of Health of the Kyrgyz Republic, Bishkek Osh Interregional United Clinical Hospital, Osh, Kyrgyz Republic // Journal Clinical medicine of kazakhstan. – No. 3 (29) 2013. – Pp. 40-41.

REVIEW ARTICLE

IRSTI 76.29.30 https://doi.org/10.26577/IAM.2022.v3.i2.08

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«SGLT2 INHIBITORS: RATIONALE FOR THE USE IN HEART FAILURE», RESOLUTION ON THE RESULTS OF THE PANEL OF EXPERTS WITH INTERNATIONAL PARTICIPATION, ALMATY

Patients with heart failure have a high risk of developing cardiovascular complications, and prevention of thereof requires timely medical care and diagnostic assessment. An expert meeting was held with the participation of the NGO "Society of Specialists in Arterial Hypertension and Cardiovascular Prevention", NGO "Evidence-Based Cardiology", NGO "Association of Endocrinologists of Kazakhstan". On April 29, 2022 a panel of experts discussed the rationale for the use of SGLT2 inhibitors in heart failure. The EMPEROR-Reduced and EMPEROR-Preserved trials analyzed cardiovascular and renal outcomes in empagliflozin treatment in patients with and without type 2 diabetes mellitus (T2DM). Several proposals and recommendations have been adopted for further research on the cardiovascular and renal effects of empagliflozin and its use in clinical practice in patients with chronic heart failure, regardless of the presence of type 2 diabetes.

At the experts meeting, issues were considered on the creation of heart failure rooms in outpatient settings and the possibility of studying the concentration of brain natriuretic peptides and performing echocardiography, including the assessment of left ventricular deformity and electrocardiography (ECG).

Key words: ECG, diabetes mellitus, CHF.

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Chronic heart failure (CHF), as one of the cardiovascular complications, is among the most common causes of death in patients and repeated hospitalizations, representing a great burden on the healthcare system. Despite the existence of proven therapies, the prognosis of patients suffering from chronic heart failure (CHF) remains unfavorable [1-4] (Fig. 1).

During a 10-year follow-up period, a patient hospitalized once with a diagnosis of de novo CHF has some limited number of hospitalizations for CHF [3]. The repeated hospitalization frequency graph is a two-phase curve that has 2 peaks: the first peak, the early one, is due to an increase in the number of hospitalizations for decompensation in the first 2-3 months after the diagnosis of CHF (up to 30% of hospitalizations are formed in this time interval) [2]. The second peak of hospitalizations is formed 2-3 months before death, and it accounts for about half of hospitalizations.

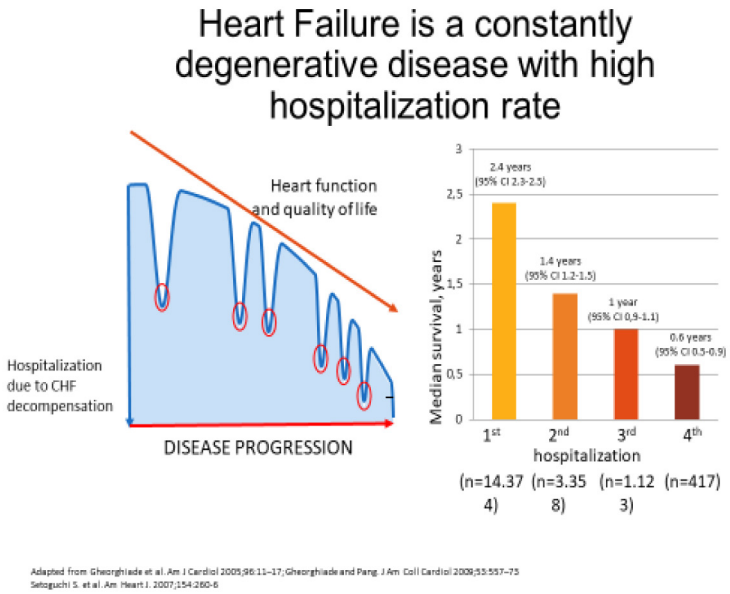
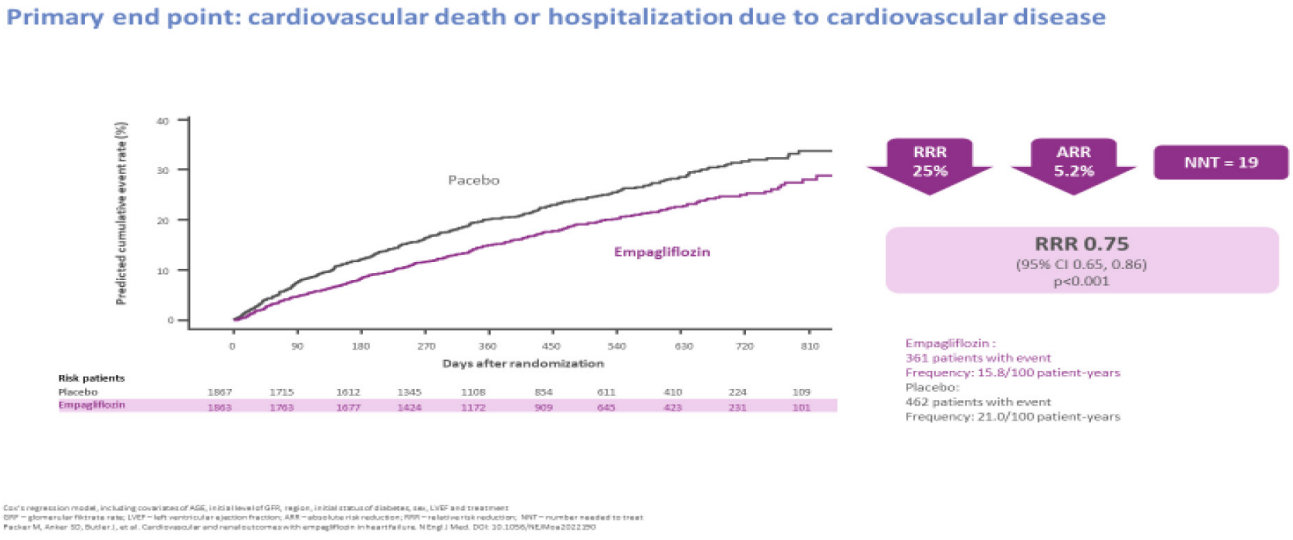


Figure 1 – Heart failure is a steadily progressive disease with a high rate of hospitalization [1]

Between them there is a "plateau phase", which lasts for years, and the frequency of rehospitalizations during this time is 15-20% of the total number of rehospitalizations. Thus, it is obvious that the longer the patient remains in the plateau phase, the longer his life expectancy will be. With each subsequent hospitalization, the functional reserves of the myocardium are significantly reduced and are not restored to their original values over time. At the same time, the risk of death with each re-hospitalization increases on average by 3.6 times [5].

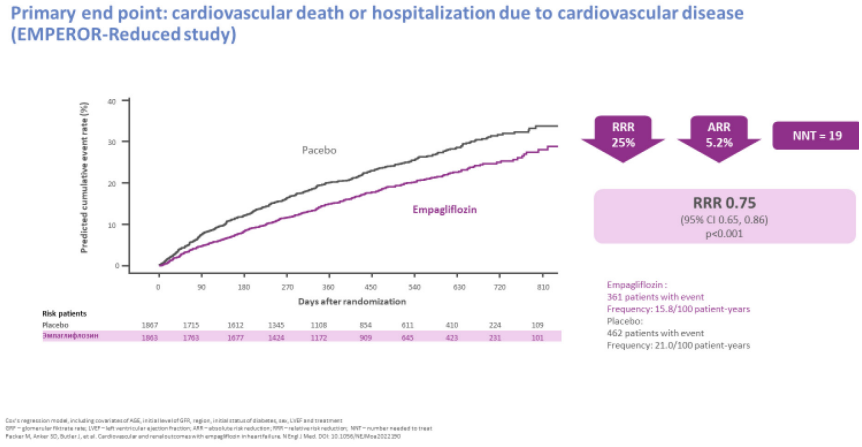


Packer M, Anker SD, Butler J.
Cardiovascular and renal outcomes with empagliflozin in heart failure [6].

In patients with type 2 diabetes mellitus (DM), sodium glucose linked cotransporter type 2 (iSGLT-2) inhibitors significantly reduce the risk of heart failure (HF) and progression of chronic kidney disease (CKD), showing benefits that no other group of antidiabetic drugs has. In major randomized placebo-controlled trials, the risk of hospitalization for heart failure in patients treated with iSGLT-2 was 30-35% lower than in the placebo group.

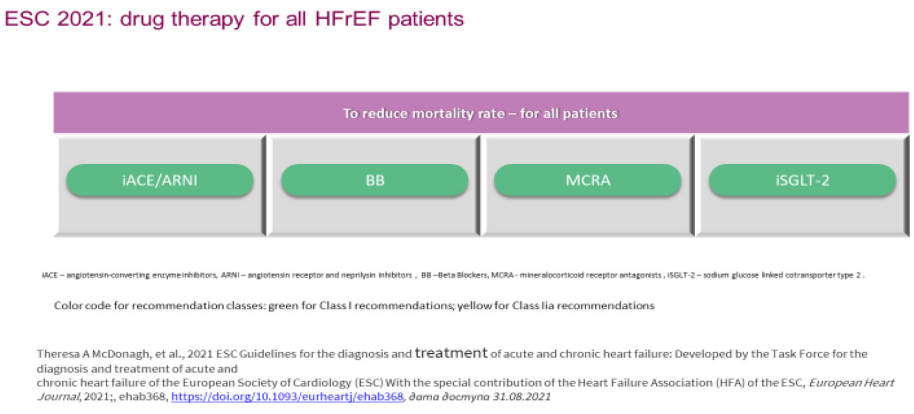
This effect was more evident in the group of patients with left ventricular ejection fraction (LVEF) <30% [5,7]. In addition, the risk of CKD progression (including death from renal causes, initiation of dialysis, and kidney transplantation) was 35–50% lower among patients treated with iSGLT-2 in current combination therapy compared with those treated with placebo. These cardiorenal effects cannot be explained by the glucose-lowering effect of iSGLT-2 alone, as drugs with greater antihyperglycemic efficacy do not show similar tendencies [8]. As a result of this observation, a hypothesis was formed that iSGLT-2 can have a cardioprotective and nephroprotective effect, regardless of the cause of damage to the heart or kidneys, and also regardless of the presence or absence of DM.

One of the latest breakthroughs in the treatment of patients with CHFrEF was the EMPEROR-Reduced study, in which empagliflozin significantly affected the primary endpoint (relative risk reduction of cardiovascular death or hospitalization due to heart failure (HF) by 25%, absolute – by 5.2%), and secondary endpoints regarding hospitalizations for HF and renal dysfunction [9-10].



Packer M, Anker SD, Butler J. Cardiovascular and renal outcomes with empagliflozin in heart failure [6].

A modern strategy for the treatment of CHFrEF is a quadrupletherapy – the use of 4 main components that affect the prognosis in patients: an angiotensin receptor and neprilysin inhibitors (ARNI), angiotensin-converting enzyme inhibitors (iACE), angiotensin 2 receptor antagonists (ARA2), (2) sodium glucose cotransporter 2 inhibitors (iSGLT2), beta-blockers (BB), ivabradine and AMP.



Theresa A., Mc Donagh 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure [2].

As of today, heart failure with preserved ejection fraction (HFpEF) is one of the largest unmet needs for cardiovascular disease therapy due to its prevalence, poor outcomes and lack of clinically proven effective treatments [11].

The results of the EMPEROR-Preserved study showed that empagliflozin demonstrated a 21% relative risk reduction for the combined primary end point of cardiovascular death or hospitalization for heart failure in adults with heart failure with preserved ejection fraction (HFpEF) compared with placebo [12- 13]. An analysis of the key secondary endpoints of the study showed that empagliflozin also reduced the relative risk of first and readmission for heart failure by 27% and slowed the decline in kidney function. It is being noted that empagliflozin shows these results in patients with any type of heart failure, regardless of ejection fraction or the presence of diabetes mellitus.

The AHA/ACC/HFSA American Cardiology Society has identified the positions of the so-called "quadrotherapy" for patients with CHF with reduced EF: SGLT2 inhibitors, beta-blockers, mineralocorticoid receptor antagonists and drugs that block the RAAS. From the latter group, it is preferable to use sacubitril / valsartan, if this is not possible – ACE inhibitors (in patients with angioedema or cough – ARA2). For CHF patients with slightly reduced ejection fraction ("HF with mildly reduced ejection fraction (HFmrEF)"), SGLT2 inhibitors have class IIa recommendations, all other drugs listed above are IIb [14-17].

During the discussion with active participation of the invited experts and the exchange of views the following issues were discussed: choice of therapy, specialists' prescriptions, availability of diagnostic methods and updating protocols for the treatment of HF.

The experts noted that according to the EMPEROR-REDUCED and EMPEROR-Preserved studies iSGLT-2, in particular empagliflozin, has certain advantages over the traditional four classes of drugs in the treatment of CHF (beta-blockers, inhibitors of the renin-angiotensin-aldosterone system, mineralocorticoid receptor antagonists, ARNI). These advantages include a single dose administration of the drug in one recommended dose, which eliminates the need for drugs titration, the absence of a significant effect on hemodynamics, the presence of proven cardioprotective and nephroprotective effects.

The experts expressed the general opinion that iSGLT-2 should be prescribed in accordance with the indications for use and the above recommendations by any of the specialists: a general practitioner, cardiologist or endocrinologist, taking into account known restrictions and as appropriate to the patient.

Patients with heart failure have a high risk of developing cardiovascular complications. To prevent them, timely medical care and timely diagnosis of heart failure is required. In this connection, there were discussed issues of creating heart failure rooms in outpatient environment and available studies regarding concentration of brain natriuretic peptides and performing echocardiography, including the assessment of left ventricular deformity and electrocardiography (ECG)

Further to the discussions during the Scientific meeting and discussions, the need for the following activities was recognized.

- Development of recommendations for cardiologists and general practitioners in the form of "pocket book" for HF patients' care assisted by a multidisciplinary team
- Arrangement of workshops for cardiologists, primary health care as part of creation of HF rooms
- Update of CHF treatment standards as per international recommendations of AHA/ACC/HFSA (2022)
- Inclusion of iSGLT2 into the list of medications and medical devices for government-funded and medicine assistance scheme at inpatient or outpatient level as part of the state benefit package for HF patients.

References

1. Adapted from Gheorghiade et al. Am J Cardiol 2005;96:11–17; Gheorghiade and Pang. J Am Coll Cardiol 2009;53:557–73

2.Theresa A McDonagh, et al., 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC, European Heart Journal, 2021; ehab368, https://doi.org/10.1093/eurheartj/ehab368

3. Crespo-Leiro MG, Metra M, Lund LH, Milicic D, Costanzo MR, Filippatos G, Gustafsson F, Tsui S, Barge-Caballero E, De Jonge N, Frigerio M, Hamdan R, Hasin T, Hulsmann M, Nalbantgil S, Potena L, Bauersachs J, Gkouziouta A, Ruhparwar A, Ristic AD, Straburzynska-Migaj E, McDonagh T, Seferovic P, Ruschitzka F. Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2018; 20:1505—1535.

4. Pieske B, Tschope C, de Boer RA, Fraser AG, Anker SD, Donal E, Edelmann F, FuM, GuazziM, LamCSP, LancellottiP, MelenovskyV, MorrisDA, Nagel E, Pieske-Kraigher E, Ponikowski P, Solomon SD, Vasan RS, Rutten FH, Voors AA, Ruschitzka F, Paulus WJ, Seferovic P, Filippatos G. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algo- rithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur Heart J 2019;40:3297—3317.

5. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. Circulation 2018;138:861 —870.

6.Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. DOI: 10.1056/NEJMoa2022190

7. Lancellotti P, Pellikka PA, Budts W, Chaudhry FA, Donal E, Dulgheru R, Edvardsen T, Garbi M, HaJW, Kane GC, Kreeger J, Mertens L, Pibarot P, Picano E, Ryan T, Tsutsui JM, Varga A. The clinical use of stress echocardiography in non-ischaemic heart disease: recommendations from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. Eur Heart JCardiovasc Imaging 2016;17:1191 —1229.

8. Januzzi JL Jr, Chen-Tournoux AA, Christenson RH, Doros G, Hollander JE, Levy PD, Nagurney JT, Nowak RM, Pang PS, Patel D, Peacock WF, Rivers EJ, Walters EL, Gaggin HK, ICON-RELOADED Investigators. N-terminal pro-B-type natriuretic peptide in the emergency department: the ICON-RELOADED study. Jam Coll Cardiol 2018;71 :1191 —1200.

9. Lainscak M, Blue L, Clark AL, Dahlstrom U, Dickstein K, Ekman I, McDonagh T, McMurray JJ, Ryder M, Stewart S, Stromberg A, Jaarsma T. Self-care management of heart failure: practical recommendations from the Patient Care Committee of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2011;13:115 —126. McDonagh TA, Blue L, Clark AL, Dahlstrom U, Ekman I, Lainscak M, McDonald K, Ryder M, Stromberg A, Jaarsma T, European Society of Cardiology Heart Failure Association Committee on Patient Care. European Society of Cardiology Heart Failure Association Standards for delivering heart failure care. EurJ Heart Fail 2011;13:235 — 241.:

10. Theresa A McDonagh, Marco Metra, Marianna Adamo, et al., 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: supplementary data. European Heart Journal (2021) 00, 1-42. doi:10.1093/eurheartj/ehab368

11. John J V McMurray, Milton Packer How Should We Sequence the Treatments for Heart Failure and a Reduced Ejection Fraction? A Redefinition of Evidence-Based Medicine. Circulation. 2021 Mar 2;143(9):875-877. doi: 10.1161/CIRCULATIONAHA.120.052926. Epub 2020 Dec 30.

12. Mueller C, McDonald K, de Boer RA, Maisel A, Cleland JGF, Kozhuharov N, Coats AJS, Metra M, Mebazaa A, Ruschitzka F, Lainscak M, Filippatos G, Seferovic PM, Meijers WC, Bayes-Genis A, Mueller T, Richards M, Januzzi JL Jr, Heart Failure Association of the European Society of Cardiology. Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. Eur J Heart Fail 2019;21:715 —731.

13. Januzzi JL, van Kimmenade R, Lainchbury J, Bayes-Genis A, Ordonez-Llanos J, Santalo-Bel M, Pinto YM, Richards M. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the International Collaborative of NT-proBNP Study. Eur Heart J2006;27:330—337.

14. Lancellotti P, Galderisi M, Edvardsen T, Donal E, Goliasch G, Cardim N, MagneJ, Laginha S, Hagendorff A, Haland TF, Aaberge L, Martinez C, Rapacciuolo A, Santoro C, Ilardi F, Postolache A, Dulgheru R, Mateescu AD, Beladan CC, Deleanu D, Marchetta S, Auffret V, Schwammenthal E, Habib G, Popescu BA. Echo-Doppler estimation of left ventricular filling pressure: results of the multi- centre EACVI Euro-Filling study. Eur Heart J Cardiovasc Imaging 2017;18:961 —968.

15. Galderisi M, Cosyns B, Edvardsen T, Cardim N, Delgado V, Di Salvo G, Donal E, Sade LE, Ernande L, Garbi M, Grapsa J, Hagendorff A, Kamp O, MagneJ, Santoro C, Stefanidis A, Lancellotti P, Popescu B, Habib G, EACVI Scientific Documents Committee. Standardization of adult transthoracic echocardiography reporting in agreement with recent chamber quantification, diastolic function, and heart valve disease recommendations: an expert consensus document of the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2017;18:1301 —1310.

16. Chronic heart failure in adults: diagnosis and management NICE (National Institute for Health and care Excellence) guideline Published: 12 September 2018 nice.org.uk/guidance/ng106;p1-p38.

17. Petar M. Seferovic, PiotrPonikowski, Stefan D. Anker; Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of The Heart Failure Association of the European Society of Cardiology; doi: 10.1002/ejhf.1531.

IRSTI 76.29.48 https://doi.org/10.26577/IAM.2022.v3.i2.09

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IMPACT OF COVID-19 ON PREGNANCY (REVIEW)

SARS-CoV-2 infection during pregnancy is associated with a number of adverse pregnancy outcomes, including preeclampsia, preterm birth, and stillbirth, especially among pregnant women with severe COVID-19. Several fetal complications such as early pregnancy loss, delivery of a premature fetus, preeclampsia, fetal death, vertical transmission, intrauterine growth retardation, and congenital structural anomalies in association with COVID-19 disease have been investigated.

To review on the fetal adverse outcome that is likely to occur during COVID-19 disease. The fetal detrimental outcomes that have been widely studied in the literature include preterm birth, stillbirth, vertical transmission. The evidence in the literature supports that there is a higher rate of preterm birth and stillbirth in women who tested positive for SARS-CoV-2 but their association with the disease is not completely clear. Furthermore, the emergence of other possible outcomes is not conclusively stated. Hence more studies are required to establish their association with COVID-19 disease to decrease and mitigate the risk of detrimental fetal outcomes through early interventions and preventive measures.

Keywords: COVID-19, pregnancy, perinatal adverse outcome, vertical transmission, congenital malformation.

Introduction

The study of the effect of SARS CoV-2 infection on various organs and systems, including reproductive organs, is of scientific and practical interest. SARS-CoV-2 infection during pregnancy is associated with a number of adverse pregnancy outcomes, including preeclampsia, preterm birth, and stillbirth, especially among pregnant women with severe COVID-19. In addition to the direct impact of COVID-19 on pregnancy outcomes, it is also of interest to study in the long term the impact of SARS-CoV-2 on the gestation process.

Members of coronaviruses (SARS-CoV, SARS-CoV-2, and MERS-CoV) have been known to have maternal-fetal complications during pregnancy. However, the detrimental maternal-fetal outcomes of MERS-CoV were more hazardous among all of them [1]. Maternal adaptations and physiologic changes in systems particularly immunological alteration during pregnancy make both mother and fetus susceptible to SARS-CoV-2 [2]. The risk of obtaining infection with SARS-CoV-2 in pregnant women is 15 times more likely than in non-pregnant women [3] and high-risk pregnancies are almost 3 times more prone rather than low-risk pregnancies [4]. According to a report published by CDC (Center for Disease Control and Prevention) in 2020, the risk of ICU admission, mechanical ventilation, and death were 3, 2.9, and 1.7 times higher in pregnant women than in their non-pregnant counterparts, respectively [5].

The Fetus can be affected during different stages of intrauterine life [6]. However, the level of detrimental fetal outcomes is related to the age of the fetus [7]. In addition, the severity of adverse perinatal outcomes is relevant to the severity of the maternal disease. The rate of severe maternal-fetal outcome is 4 times higher in severe-critical cases that required ICU admission and maternal respiratory support rather than in mild-moderate or asymptomatic cases [8,9].

The potential mechanisms responsible for fetal complications in pregnant women with SARS-Cov-2 are not fully understood. However published literature demonstrated that persistent expression of angiotensin converting enzyme-2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) receptors during the entire pregnancy facilitated the entry of the virus to the placental cells [10], abnormal placental inflammatory histopathologic changes including feto-maternal vascular malperfusion, intervillous fibrin deposition and villitis of unknown etiology were associated with the disease [11,12]. Furthermore, triggered pro-inflammatory and anti-inflammatory states of pregnancy (cytokine storm) throughout different stages of intrauterine life contribute to Th1/Th2 imbalance, and supra-physiologic levels of cytokines are involved in the

adverse perinatal outcome of the disease [10, 13]. In addition to the direct effect of SARS-Cov-2, the lockdown rules during the pandemic such as reducing or virtual pattern of medical services and late attending of the pregnant woman to the hospitals, fear of exposure to or spreading the infection, allocation of nearly all health facilities for COVID-19 patients, reducing public transport can indirectly impact the outcome of pregnancies, particularly for high-risk patients that need increased antenatal services [14, 15].

There is a wide range of fetal complications that have been studied with covid-19 disease including miscarriage, stillbirth, growth restriction, preterm labor, vertical transmission, and congenital malformation. The purpose of this review is to focus on their emerging, frequency likelihood mechanism of development, and their relation to the severity of the disease. Moreover, this literature review gives an overview of the available evidence, points up the controversies, and helps the researchers to understand where to put their efforts in further research. This review can be an informative document for health care providers practicing medicine in all fields and pregnant women themselves.

To carry out this literature review, a search was performed using different databases such as Google Scholar and PubMed. The most relevant and recent articles related to different complications were selected. Original articles and systematic reviews were prioritized. However, for some complications, there were only case reports and case series available. The review is organized in sections, each section is intended to give an overview of the outcome, their association with the covid-19 disease, and the possible mechanism that they can develop.

Miscarriage

The association between previous coronaviruses (SARS-Cov and MERS-Cov) and adverse pregnancy outcomes including spontaneous abortion (termination of pregnancy less than 20 weeks of gestation) has been previously demonstrated [16]. The reported rate of abortion that was related to SARS-Cov in the 2002-2003 years was 57% and the adverse outcome of MERS-COV was more crucial [17]. Hence some authors tried to study the impacts of COVID-19 disease on the rate of first-trimester pregnancy loss. Gestational age at the time of infection is an independent risk factor for adverse fetal outcomes. The rate of adverse fetal outcomes is significantly higher in the first 12 weeks of pregnancy compared to second and third trimesters (35.3 vs. 2%, $p<0.001$) [7]. Cavalcante et al concluded in their systemic review and meta-analysis that the rate of miscarriage in pregnant women infected with SARS-Cov-2 was estimated at 15% and 23% using fixed and random effect models, respectively. However, their findings were not compared with pregnant women without SARS-Cov-2 infection [8]. A retrospective cohort study conducted by Sacinti et al including 1269 pregnancies compared the rate of miscarriages between the years 2019 and 2020. These authors found that the rate of miscarriage was 25% higher in the year 2020 than in 2019, but the increase in the rate could be related to a reduced number of overall pregnancies during the pandemic than in the pre-pandemic period (542 vs 727) or reduced attending of pregnant women due to lockdown rules since only 4.7 of women with miscarriage tested positive for SARS-Cov-2 [18]. Accordingly, another systematic review concluded that the risk of early and late spontaneous abortions increased in pregnant women who tested positive for SARS-Cov-2 and had no comorbidities or risk factors for abortion. However, all the included studies were between case reports and case series that suggest larger studies [19].

Conversely, Cosma et al in a case-control study at St. Anna hospital in 2020 indicated that there were no significant differences in the rate of SARS-Cov-2 positivity in both cases and the control group (11% vs 9.6) [20].

Hence the ACE2 and TMPRSS2 receptors do not express or are low up to 24 weeks of pregnancy [21] it appears that SARS-Cov-2 similar to previous coronaviruses (SARS-Cov) may act in an indirect pattern and provoke immune responses. The secondary triggered pro-inflammatory state is accompanied by high levels of IL-6, IL-8, TNF-alpha, and other cytokines. The established cytokine storm interferes with trophectoderm-endometrium molecular signaling and disrupts decidualization and trophoblastic invasion resulting in implantation failure. Furthermore, the associated hypercoagulable state produces microvascular thrombus formation in a preterm undeveloped placenta that results in an inappropriate intrauterine environment for a developing vulnerable embryo in the first trimester of pregnancy [13]. However, there was a case of 13 weeks spontaneous abortion reported the existence of viral N protein and signals for viral replication, RNA genome synthesis and surface spike proteins in the placenta and fetal tissues detected by Immunofluorescence and electron microscopy [12].

Summary of characteristics and results from some studies on miscarriage was presented on table 1.

Table 1 – Summary of characteristics and results from some studies on miscarriage

Author	Type of study and population	Objectives	Main outcomes	Results
Sacinti et al. (2020)	retrospective cohort study 1269 pregnancy	Compare the risk of early fetal loss during the pandemic to the pre-pandemic period	Early pregnancy loss was increased during the pandemic period	IRR 1.25 (95% CI, 1.16–1.35, *P*<0.0001)
Cosma et al. (2020)	Case-control studies 225 first trimester pregnancies (100 cases of spontaneous abortions and 125 normal ongoing pregnancies)	Demonstrate whether SARS-Cov-2 is a risk factor for early pregnancy loss	Exposure to SARS-Cov-2 in early pregnancy does not predispose to early pregnancy loss	OR 1.28 (95%CI 0.53-3.08, P=0.73)

Stillbirth

Stillbirth (intrauterine death of the fetus after 28 weeks of pregnancy but before birth) and the correlation with SARS-Cov-2 infection throughout the pregnancy have been widely studied. Pieces of evidence indicated that the rate of stillbirth increased during the pandemic than the pre-pandemic epoch. De Sisto and colleagues concluded in their study that the risk of stillbirth was nearly 2 times higher in pregnant women with COVID-19 disease compared to the pregnant population not exposed to the infection, particularly during the period of the Delta wave the rate was 4 times higher in infected pregnant women [22].

When evaluating the risk of stillbirth in pregnant women with COVID-19 in England, Urganci et al explored that fetal death was almost 2.5 times more likely in laboratory-confirmed SARS-Cov-2 infected pregnant women with a rate of 8.5 per 1000 birth versus a rate of 3.4 per 1000 birth in pregnant women without the disease [23]. Likewise, Khalil and colleagues found in their study at St. George's University Hospital, London that the rate of stillbirth was 2.38 per 1000 births in the pre-pandemic period versus 9.31 per 1000 births in the pandemic period. Although there were no cases of COVID-19 disease among pregnant women with stillbirth, it seems that lockdown rules contributed to the increased rate, particularly in high-risk pregnancies that required early intervention [15]. This is in concordance with the result obtained from a study conducted in four Indian hospitals. The authors found that despite a 43.2% reduction in hospitalization rate and 66.4% reduction in referred emergency obstetric case rates in tertiary care centers during the lockdown period, there was an increased rate of stillbirth compared to the pre-lockdown period (3.15 vs 2.25%) [14].

Some authors tried to study the correlation between the severity of maternal disease and fetal adverse outcomes. In a large cohort study encompassing data from the Premier Healthcare Database (20% of US hospitalization) Jering et al concluded that the stillbirth rate was 1.5 times higher in women with the covid-19 disease who give birth. However, their finding was not statistically significant. They also demonstrated that the rate of stillbirth was 8 times more likely in cases that required mechanical ventilation or in-hospital maternal deaths cases [24].

Characteristics and results from studies about stillbirth were presented on table 2.

Table 2 – Characteristics and results from studies about stillbirth

Author	Type of study and population	Objectives	Main outcomes	Results
De Sisto et al 2021	Retrospective study 1,249,634 pregnancy	Compare the risk of stillbirth in pregnant women with and without COVID 19	Higher Stillbirth rates were strongly associated with the Delta variant of SARS-Cov-2	aRR, 4.04 (95% CI, 3.28–4.97)
Gurol-Urganci et al 2021	Population-based cohort study 3527 women	Study of the association of SARS-Cov-2 and perinatal adverse outcome at the time of birth	laboratory-confirmed SARS-Cov-2 infected pregnancies was associated with higher rates of fetal death	aOR 2.21 (95% CI, 1.58-3.1, P<.001)
Jering et al 2021	Retrospective cohort study 406446 women	Study the clinical characteristics and severity of the outcome of women with and without COVID 19	Stillbirth was higher in SARS-Cov-2 positive pregnant women The risk is even more in women with respiratory support	aOR 1.23 (95% CI, 0.87-1.75) OR 7.88 (95% CI, 2.39- 25.98)

Vertical transmission of SARS-Cov2

Transplacental transmission of the SARS-Cov-2 has not been conclusively stated. There are controversies in studies on vertical transmission of the disease. Placenta has an important role in protecting the fetus. The Syncytia-Capillary Barrier (SCB) in the placental villas prevents the entrance of the virus into the fetal circulation by having strong intercellular junctions. On the other hand, lack of Caveolins expressions (a plasma membrane protein in syncytiotrophoblasts responsible for activation of inflammatory pathways in the cells) prevents inflammatory mediated damage of the barrier by cells that were able to enter the syncytiotrophoblasts and vertical transmission of SARS-Cov-2 [21].

To assess the possibility of maternal-fetal transmission of SARS-Cov-2 Arora and colleagues found in their prospective pilot study that RT-PCR test of cord blood samples during vaginal delivery and test of amniotic fluid in addition to the cord blood sample in cesarean deliveries collected in a sterile manner were negative in all neonates born from SARS-Cov-2 positive mothers. Moreover, the authors repeated the throat and nasopharyngeal swab RT-PCR tests of newborns 24-48 hours after delivery, despite they were room in with their mothers the tests showed negative results [25]. The transmission of SARS-Cov-2 infection in midterm alive intrauterine pregnancies also have been studied. Yu et al reported 2 cases of second-trimester pregnancy with a history of COVID-19 disease that had undergone amniocentesis. The amniotic fluid sample RT-PCR test, as well as SARS-Cov-2 IgG and IgM, showed a negative result. [26] Similar to the above research, a retrospective cohort study conducted by Patberg et al at NYU Winthrop Hospital concluded that despite degrees of placental histopathological changes in pregnant women who tested positive for SARS-Cov-2 infection, the RT-PCR tests of their neonates were negative [27].

Considering the above studies maternal-fetal transmission is unlikely not only in the term but also in midterm pregnancies. However, there are some reported cases of SARS-Cov-2 vertical transmission. Transmission of the virus from the mother to the fetus may be dependent on fetal genetic factors, SARS-Cov-2 genetic variants, and high maternal viral load [28].

Vazquez et al studied a case of spontaneous abortion in a pregnant woman infected with SARS-Cov-2. The researchers detected viral N protein, signals for viral replication, RNA genome synthesis, and surface spike proteins in the placenta and fetal lungs and kidneys with the use of Immunofluorescence and electron microscopy analysis [12]. A similar case was reported by Facchetti et al studying 15 cases of SARS-Cov-2 infected mothers undergoing delivery where the authors identified only one case of neonatal RT-PCR positive test that progressed to pneumonia twenty-four hours after birth. In addition, viral N and S proteins were also detected in the placenta at the time of birth [28].

Preterm delivery

Prematurity is the primary contributor to mortality among children under 5 years of age. The short and long-term complications of preterm birth contribute to an estimated 1 million death of children each year [29]. Hence establishing the association between SARS-Cov-2 infection and the risk of preterm labor and prematurity is in high priority. Diriba and colleagues in their systematic review and meta-analysis including 25 studies in developed countries found that the rate of preterm birth at <37 weeks in pregnant women with the covid-19 disease increased to 14.3% [16]. Whereas the rate of preterm birth ranges from 5% in high-income countries to 18% in low-income countries [29]. A population-based cohort study in California showed that SARS-Cov-2 infection during pregnancy was associated with 40% increased odds of preterm birth, and 60% increased odds of very preterm birth. The rates of preterm birth and very preterm birth were even higher in pregnant women with the COVID-19 disease and maternal comorbidities. Furthermore, the COVID-19 disease was associated with a 50% increase in the rate of spontaneous preterm labor and a 30% increase in induced preterm labor [30]. However, a multinational cohort study demonstrates a different result with medically indicated preterm delivery the most common type of birth (83%) in pregnant women infected with SARS-Cov-2 rather than spontaneous preterm birth and hypertensive disorders of pregnancy constituted 24.7%, the leading cause of induction [31].

The risk of preterm birth is strongly associated with the severity of the maternal disease. Shu Qin Wei et al conducted a systematic review and meta-analysis on the effect of COVID-19 disease on pregnancy outcomes. The authors also compared the extent of adverse fetal outcomes according to the severity of SARS-Cov-2 infection. The results showed that the risk of preterm birth was 1.8 times higher in pregnant women with COVID-19 disease than in those without. In symptomatic pregnant women, the risk was 2.29 times more likely than in asymptomatic patients and the likelihood of preterm birth was elevated to 4 times in severe cases compared to mild COVID-19 cases [32].

Implementation of mitigation measures for the prevention of SARS-Cov-2 can reduce the incidence of preterm birth. Following a large national quasi-experimental study, Been and colleagues concluded that preventive measures for COVID-19 were associated with a significant reduction of preterm birth rate throughout all gestational ages with a more apparent, effective, and statistically significant for the gestational ages of 23 weeks-36 weeks ± 6 day [33]. Reduced exposure to infection and physical activity due to the changing work environment and pattern impacted the rate of preterm birth particularly very preterm birth and extremely very low birth preterm birth [33, 34].

The cause of preterm birth in pregnant women infected with SARS-Cov-2 is likely related to the exaggerated systemic inflammatory state [10], maternal vascular damage that contributes to preeclampsia, IUGR, and fetal distress as a consequence of medically initiated preterm birth [11,31], and fetal vascular injury damage [27].

Characteristics and results from some studies about preterm birth were presented on table 3.

Table 3 – Characteristics and results from some studies about preterm birth

Author	Type of study and population	Objectives	Main outcomes	Results
Shu Qin Wei	Meta-analysis including 42 studies	Study the association between SARS-Cov-2 and adverse pregnancy outcome	Preterm birth in SARS-Cov-2 infected pregnant women vs non-infected Symptomatic vs asymptomatic Severe cases vs mild cases	(OR 1.82, 95% CI 1.38 to 2.3) (OR 2.29, 95% CI 1.49 to 3.53) (OR 4.29, 95% CI 2.41 to 7.63)
Karasek et al	Population-based cohort study 240,157 pregnant women with live births	Study the effect of the covid-19 pandemic on the rate of preterm birth	Very preterm + comorbidities Preterm + comorbidities	aRR 1.6 (95% CI 1.3, 2.0) aRR 2.6 (2.1, 3.1) aRR 1.3(95% CI 1.2, 1.5) aRR 2.0 (1.8, 2.2)
Villar J et al	Prospective cohort study 2130 pregnant women	Evaluation of risks in pregnancy with COVID-19 compared with not-infected pregnant patients	Preterm birth	RR 1.59 (95% CI 1.30 to 1.94)

Intrauterine growth retardation

One of the adverse fetal outcomes of COVID-19 disease that have been investigated is intrauterine growth retardation. Fetal growth retardation is associated with stillbirth, neonatal death, and long-term neonatal complications. Maternal-fetal infections and placental diseases including placental insufficiency can account for fetal growth delay [35].

Eltemamy et al conducted a pilot case-control study to establish the correlation between SARS-Cov-2 exposure and the risk of both fetal growth retardation and structural anomaly. The authors found no significant differences in fetal growth parameters, Doppler study, and rate of gross structural anomalies in regular antenatal visits of the cases group (pregnant women with no risk factors, normal nuchal translucency, and history of confirmed positive SARS-Cov-2 in their first trimester) compared to controls group.[36] Similar results were found in a retrospective cohort study where Narang et al also concluded that there were no significant differences in the rate of intrauterine growth retardation rate in mild or asymptomatic SARS-Cov-2 infected pregnant women, irrespective of the timing of infection, compared to those with a negative infection result (3.4% vs 4.8%, p=0.36) [37].

Conversely, following a case-control study Anuk and colleagues found that the pulsatility index and resistance of umbilical artery and uterine artery of low-risk pregnant women with a history of COVID-19 disease 3 weeks after the quarantine was remarkably higher than women with no history of exposure to SARS-Cov-2 [38]. Whereas umbilical artery Doppler study is a strong assessment method for predicting IUGR in high-risk pregnancies [39]. The likelihood of intrauterine growth retardation manifestation in the later stage of pregnancy could not be excluded. Furthermore, Kumar et al found a case of intrauterine growth retardation associated

with severe oligohydramnios and loss of fetal movement in a term pregnancy with a history of positive SARS-Cov-2 at 32 weeks gestation. Hence the woman had no risk factors for fetal growth delay and the antenatal follow-ups were normal up to 32 weeks, SARS-Cov-2 was assumed to be the cause [40].

Despite the placental histopathologic changes contributing to placental ischemia in pregnant women with positive SARS-Cov-2 have been widely investigated. None of the studies has acknowledged the association between placental changes and fetal growth retardation [11,27].

Congenital anomalies

Viral infections in pregnancy are known to be associated with congenital malformations. It is still fully unknown whether SARS-Cov-2 infection, anti-COVID-19 therapy, or vaccination during pregnancy have an adverse effect on the growing fetus or not [41,42]. There is a lack of enough evidence to conclude the risk of structural malformation in women with a history of positive SARS-Cov-2 throughout their pregnancy. Perveen et al reported a case of limb structural deformation due to ischemia and gangrene in a preterm 33 weeks neonate born of a mother with a history of positive SARS-Cov-2. However, the author did not find any thromboembolic events in the placenta or neonatal vasculature, and also there were no risk factors in neonates for in utero thromboembolism and the skin tissue specimen was negative for infections thus the possible association between SARS-Cov-2 and limb gangrene could not be ruled out [43]. On the other hand, SARS-Cov-2 and the associated hyperinflammatory and hypercoagulable state may lead to ischemic limb injury in adults [44].

There is a hypothesis that exposure to SARS-Cov-2 during organogenesis may affect the developing fetus and increase the risk of structural anomalies and neural tube defects. ACE2 receptors that exist in the zygote and uterus facilitate the viral entry to the replicating cells. Moreover, placental vascular malperfusion with fetal hypoxia, [45] induced maternal systemic illness such as hyperthermia, and antiviral medication [42] might have a neurodevelopmental adverse effect on the growing fetus.

Some authors reported cases of organ injury in neonates born from mothers exposed to SARS-Cov-2 in utero [45]. While others did not find any congenital malformation even though there were the findings of viral particles and signs of viral replication in neonatal tissue examinations [12].

Almost all of the studies on the impact of COVID-19 disease on congenital anomalies are confined to the case reports and case series that recommend large studies to confirm the association between SARS-Cov-2 and the risk of congenital anomalies [43, 45, 46].

Preeclampsia

Several studies have reported an epidemiological association between COVID-19 and preeclampsia. Two recent meta-analyses found a higher incidence of preeclampsia, severe preeclampsia, eclampsia, and HELLP syndrome in pregnant women with SARS-CoV-2 than in the general pregnant population [47, 48, 49]. In the INTERCOVID study, preeclampsia was the only condition in women with asymptomatic SARS-CoV-2 infection [31].

Conclusion and recommendations for future research

To date, there is strong evidence for the adverse effects of SARS-Cov-2 on pregnancy, with a higher incidence of severe preeclampsia, miscarriage, preterm birth and stillbirth. Finding out the association between fetal adverse outcomes and the SARS-Cov-2 during pregnancy is crucial for predicting, early intervention, and preventing complications.

Funding

This research is funded by the Science Committee of the Ministry of Education and Science of the Republic of Kazakhstan (Grant No. AP 14870089).

References

1. G. A. de Souza Silva et al. SARS-CoV, MERS-CoV and SARS-CoV-2 infections in pregnancy and fetal development. J. Gynecol. Obstet. Hum. Reprod., vol. 49, no. 10, 2020, doi: 10.1016/j.jogoh.2020.101846.

2. S. L. Dashraath P, Wong JLJ, Lim MXK, Lim LM, Li S, Biswas A, Choolani M, Mattar C. Special Report and pregnancy. Am J Obs. Gynecol, vol. 222, no. 6, pp. 521–531, 2020.

3. M. Jeannie C. Kelly, MD, M. Nandini Raghuraman, MD, and M. Ebony B. Carter, MD, Preprocedural asymptomatic coronavirus disease 2019 cases in obstetrical and surgical units. Am. J. Obstet. Gynecol., no. January, pp. 114–116, 2020.

4. A.Tanacana, S.A. Erola, B.Turgaya et al. The rate of SARS-CoV-2 positivity in asymptomatic pregnant women admitted to hospital for delivery: Experience of a pandemic center in Turkey Atakan. Eur. J. Obstet. Gynecol. Reprod. Biol., vol. 253, no. July, pp. 31–34, 2020.

5. L. D. Zambrano et al. Update: Characteristics of Symptomatic Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status – United States, January 22–October 3, 2020. MMWR. Morb. Mortal. Wkly. Rep., vol. 69, no. 44, pp. 1641–1647, 2020, doi: 10.15585/mmwr.mm6944e3.

6. E. A. N. Wastnedge et al. Pregnancy and COVID-19. Physiol. Rev., vol. 101, no. 1, pp. 303–318, 2021, doi: 10.1152/physrev.00024.2020.

7. D. Di Mascio et al. Risk factors associated with adverse fetal outcomes in pregnancies affected by Coronavirus disease 2019 (COVID-19): A secondary analysis of the WAPM study on COVID-19. J. Perinat. Med., vol. 48, no. 9, pp. 950–958, 2020, doi: 10.1515/jpm-2020-0355.

8. M. Borges, C. Torres, and D. M. Bezerra. COVID-19 and miscarriage: From immunopathological mechanisms to actual clinical evidence. vol. 148, no. september, pp. 1–12, 2021.

9. T. D. Metz et al. Disease Severity and Perinatal Outcomes of Pregnant Patients With Coronavirus Disease 2019 (COVID-19). Obstet. Gynecol., vol. 137, no. 4, pp. 571–580, 2021, doi: 10.1097/AOG.0000000000004339.

10. C. M. Seymen. Being pregnant in the COVID-19 pandemic: Effects on the placenta in all aspects. J. Med. Virol., vol. 93, no. 5, pp. 2769–2773, 2021, doi: 10.1002/jmv.26857.

11. R. Di Girolamo et al. Placental histopathology after SARS-CoV-2 infection in pregnancy: a systematic review and meta-analysis. Am. J. Obstet. Gynecol. MFM, vol. 3, no. 6, pp. 1–11, 2021, doi: 10.1016/j.ajogmf.2021.100468.

12. M. Y. Valdespino-Vázquez et al. Fetal and placental infection with SARS-CoV-2 in early pregnancy. J. Med. Virol., vol. 93, no. 7, pp. 4480–4487, 2021, doi: 10.1002/jmv.26965.

13. E. S. Sills and S. H. Wood. An Experimental Model for Peri-conceptual COVID-19 Pregnancy Loss and Proposed Interventions to Optimize Outcomes. Int. J. Mol. Cell. Med., vol. 9, no. 3, pp. 180–187, 2020, doi: 10.22088/IJMCM.BUMS.9.3.

14. R. C. Vimla Kumari, K.Mehta. COVID-19 outbreak and decreased hospitalisation of pregnant women in labour. Lancet, vol. 8, no. september, pp. 1116–1117, 2020.

15. P. Asma Khalil et al. Change in the Incidence of Stillbirth and Preterm Delivery During the COVID-19 Pandemic. Am. Med. Assoc., vol. 324, no. 7, pp. 705–706, 2020, doi: 10.1136/bmj.m2107.

16. K. Diriba, E. Awulachew, E. Getu. The effect of coronavirus infection (SARS-CoV-2, MERS-CoV, and SARS-CoV) during pregnancy and the possibility of vertical maternal-fetal transmission: a systematic review and meta-analysis. Eur. J. Med. Res., vol. 25, no. 1, pp. 1–14, 2020, doi: 10.1186/s40001-020-00439-w.

17. G. Favre, L. Ã. Pomar, D. Musso, and D. Baud. 2019-nCoV epidemic: what about pregnancies? Lancet, vol. 395, no. 10224, p. e40, 2020, doi: 10.1016/S0140-6736(20)30311-1.

18. Sacinti. K.G, E. Kalafat, and S. Y. E. And Koc. A. Increased incidence of first-trimester miscarriage during the COVID-19 pandemic. Ultrasound Obs. Gynecol, vol. 57, pp. 1006–1014, 2021, doi: 10.1002/uog.23655.

19. S. N. Kazemi et al. COVID-19 and cause of pregnancy loss during the pandemic : A systematic review. pp. 1–10, 2021, doi: 10.1371/journal.pone.0255994.

20. P. Stefano Cosma et al., Coronavirus disease 2019 and first-trimester spontaneous abortion: a case-control study of 225 pregnant patients. Am. J. Obstet. Gynecol., vol. 391, no. April, pp. 1–7, 2021.

21. O. Celik, A. Saglam, B. Baysal, I. E. Derwig, N. Celik, and M. Ak. Factors preventing materno-fetal transmission of SARS-CoV-2. Placenta J., vol. 97, no. May, pp. 1–5, 2020.

22. C. L. DeSisto et al. Risk for Stillbirth Among Women With and Without COVID-19 at Delivery Hospitalization – United States, March 2020–September 2021. MMWR. Morb. Mortal. Wkly. Rep., vol. 70, no. 47, pp. 1640–1645, 2021, doi: 10.15585/mmwr.mm7047e1.

23. I. Gurol-urganci, J. E. Jardine, F. Carroll, T. Draycott, and G. Dunn. Maternal and perinatal outcomes of pregnant women with SARS-CoV-2 infection at the time of birth in England: national cohort study. Am. J. Obstet. Gynecol., vol. 522, no. November, pp. 1–11, 2021.

24. M. Karola S. Jering et al. Clinical Characteristics and Outcomes of HospitalizedWomen Giving Birth With andWithout COVID-19. JAMA Intern. Med., pp. 1–4, 2021, doi: 10.1080/17476348.2021.1923484.

25. D. Arora et al. Assessment of materno-foetal transmission of SARS-CoV-2: A prospective pilot study. Med. J. Armed Forces India, vol. 77, pp. S398–S403, 2021, doi: 10.1016/j.mjafi.2021.01.007.

26. N. Yu, W. Li, Q. Kang, W. Zeng, L. Feng, and J. Wu. No SARS-CoV-2 detected in amniotic fluid in mid-pregnancy. Lancet Infect. Dis., vol. 20, no. 12, p. 1364, 2020, doi: 10.1016/S1473-3099(20)30320-0.

27. E. T. Patberg et al. Coronavirus disease 2019 infection and placental histopathology in women delivering at term. Am. J. Obstet. Gynecol., vol. 224, no. 4, pp. 382.e1-382.e18, 2021, doi: 10.1016/j.ajog.2020.10.020.

28. F. Facchetti et al. SARS-CoV2 vertical transmission with adverse effects on the newborn revealed through integrated immunohistochemical, electron microscopy and molecular analyses of Placenta. EBioMedicine, vol. 59, 2020, doi: 10.1016/j.ebiom.2020.102951.

29. WHO, "preterm," World Health Organization, 2018. https://www.who.int/news-room/fact-sheets/detail/preterm-birth.

30. D. Karasek et al. The association of COVID-19 infection in pregnancy with preterm birth: A retrospective cohort study in California Deborah. Lancet Reg. Heal. – Am., vol. 2, no. July, pp. 1–8, 2021.

31. J. Villar et al. Maternal and Neonatal Morbidity and Mortality among Pregnant Women with and without COVID-19 Infection: The INTERCOVID Multinational Cohort Study," JAMA Pediatr., vol. 175, no. 8, pp. 817–826, 2021, doi: 10.1001/jamapediatrics.2021.1050.

32. S. Q. Wei, M. Bilodeau-Bertrand, S. Liu, and N. Auger. The impact of COVID-19 on pregnancy outcomes: A systematic review and meta-analysis. Cmaj, vol. 193, no. 16, pp. E540–E548, 2021, doi: 10.1503/cmaj.202604.

33. Been Jasper V. et al. Impact of COVID-19 mitigation measures on the incidence of preterm preterm birth: a national quasi-experimental study. Lancet, vol. 5, no. November, pp. 604–609, 2020.

34. G. Hedermann et al. Danish premature birth rates during the COVID-19 lockdown. Arch. Dis. Child. Fetal Neonatal Ed., vol. 106, no. 1, pp. F93–F95, 2021, doi: 10.1136/archdischild-2020-319990.

35. ACOG, Practice Bullettin No 204:Fetal growth restriction. Am. Coll. Obstet. Gynecol., vol. 133, no. 1, pp. 1–25, 2019.

36. E. Eltemamy et al. Assessment of fetal growth and anomalies in the era of COVID-19 pandemic: an Egyptian pilot study. Middle East Fertil. Soc. J., vol. 26, no. 1, pp. 0–5, 2021, doi: 10.1186/s43043-021-00075-2.

37. K. Narang et al. Impact of mild COVID-19 infection on fetal growth during pregnancy. Am. J. Obstet. Gynecol., vol. 226, no. 1, pp. S321–S322, 2022, doi: 10.1016/j.ajog.2021.11.541.

38. A. T. Anuk et al. Doppler assessment of the fetus in pregnant women recovered from COVID-19. J. Obstet. Gynaecol. Res., vol. 47, no. 5, pp. 1757–1762, 2021, doi: 10.1111/jog.14726.

39. S. Khanduri et al. Role of Color Doppler Flowmetry in Prediction of Intrauterine Growth Retardation in High-Risk Pregnancy. Cureus, vol. 9, no. 11, 2017, doi: 10.7759/cureus.1827.

40. P. S. Kumar, B. Kumar, and M. M. Saha. Development of Intrauterine Growth Restriction Following Covid 19 Infection in Third Trimester of Pregnancy. J West Bengal Univ Heal. Sci, vol. 1, no. 3, pp. 71–75, 2021.

41. C. H. Fernandes, R. G. Sabongi, and J. B. G. Dos Santos. Covid-19 and Upper Limb Anomalies in Newborns: a Reason for Concern? Acta Ortop. Bras., vol. 30, no. 1, pp. 1–4, 2022, doi: 10.1590/1413-785220223001e252308.

42. M. S. I. Khan et al. Risk of congenital birth defects during COVID-19 pandemic: Draw attention to the physicians and policymakers. J. Glob. Health, vol. 10, no. 2, 2020, doi: 10.7189/JOGH.10.020378.

43. S. Perveen, K. A. Millington, S. Acharya, A. Garg, and V. Boyar. Neonate born with ischemic limb to a COVID-19 positive mother: management and review of literature. Case Reports Perinat. Med., vol. 10, no. 1, pp. 1–6, 2021, doi: 10.1515/crpm-2020-0086.

44. R. M. Putko et al. SARS-CoV-2 and limb ischemia: A systematic review. J. Clin. Orthop. Trauma, vol. 12, no. 1, pp. 194–199, 2021, doi: 10.1016/j.jcot.2020.11.018.

45. G. Favre et al. Decreased fetal movements: A sign of placental sars-cov-2 infection with perinatal brain injury. Viruses, vol. 13, no. 12, pp. 1–11, 2021, doi: 10.3390/v13122517.

46. S. Cosma et al. Prenatal biochemical and ultrasound markers in covid-19 pregnant patients: A prospective case-control study. Diagnostics, vol. 11, no. 3, pp. 1–11, 2021, doi: 10.3390/diagnostics11030398.

47. Gurol-Urganci I. et al. Maternal and perinatal outcomes of pregnant women with SARS-CoV-2 infection at the time of birth in England: national cohort study. Am J Obstet Gynecol. 2021 Nov;225(5):522.e1-522.e11. doi: 10.1016/j.ajog.2021.05.016. Epub 2021 May 20. PMID: 34023315; PMCID: PMC8135190.

48. Cruz Melguizo S. et al. Pregnancy Outcomes and SARS-CoV-2 Infection: The Spanish Obstetric Emergency Group Study. Viruses. 2021 May 7;13(5):853. doi: 10.3390/v13050853. PMID: 34067086; PMCID: PMC8151603.

49. Conde-Agudelo A, Romero R. SARS-CoV-2 infection during pregnancy and risk of preeclampsia: a systematic review and meta-analysis. Am J Obstet Gynecol. 2022 Jan;226(1):68-89.e3. doi: 10.1016/j.ajog.2021.07.009. Epub 2021 Jul 21. PMID: 34302772; PMCID: PMC8294655.

IRSTI 76.29.39 https://doi.org/10.26577/IAM.2022.v3.i2.010

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FEATURES OF LAPAROSCOPIC CHOLECYSTECTOMY IN SPECIAL GROUPS OF PATIENTS

Currently, laparoscopic cholecystectomy is the gold standard in patients with symptomatic gallstone disease. About 90% of cholecystectomies are performed laparoscopically due to faster recovery, fewer complications, cost and cosmetic effect. In this study, we evaluated the features of laparoscopic cholecystectomy in general, as well as in obese patients, aged patients, and pregnant women. Carrying out LCE in the elderly, pregnant women and obese patients today does not cause big problems. The main thing is to take into account the characteristics of each patient. In the case of LCE in the elderly, careful preoperative preparation of the vascular, hemodynamic, and respiratory status should be carried out to prevent adverse events. And the optimal period for the safest laparoscopic surgery in pregnant women is the second trimester. It is also necessary to remember that proper preparation should be carried out in consultation with obstetricians and anesthesiologists. At the same time LCE can be performed safely and effectively in patients with even a high degree of obesity showing equally good results compared to patients with normal BMI. Laparoscopic cholecystectomy is safe in patients with Child-Pugh A cirrhosis and should be used with caution in patients with Child-Pugh B cirrhosis. For patients with Class C cirrhosis, laparoscopic surgery is not recommended.

Keywords: acute calculous cholecystitis, laparoscopic cholecystectomy, open cholecystectomy, cholelithiasis (gallstone disease).

Introduction

Gallstone disease is one of the most common abdominal disorders [1]. Among diseases of the digestive system, cholelithiasis accounts for 15-20% [2,3]. However, 20-40% of patients with gallstone disease develop complications associated with gallstones as high as 1-3% per year. And in 10-15% of cases, acute calculous cholecystitis is the first clinical manifestation [4,5]. Thus, every year there is an increase in surgical interventions for calculous cholecystitis and its complications. Surgical treatment of cholelithiasis began more than 100 years ago. Over this period approaches and visions of surgical treatment have changed many times [6]. With the introduction of the laparoscopic method the length of hospital stay with cholecystectomy has decreased, and now laparoscopic cholecystectomy (LC) is widely recognized as an appropriate and safe treatment method, also due to its low invasiveness, injury rate and reduced rehabilitation period [7].

History of LCE

Erich Muhe is a German professor who performed the first ever laparoscopic cholecystectomy in 1985 using a galloscope-laparoscope he invented. But unfortunately, the medical community criticized and did not recognize the surgey he performed [8].

Today we can say that the author performed single-port cholecystectomy which was not only the first in the history of LCE, but also the first in the medical history: two years later, on March 17, 1987 Philippe Mouret was able to perform "laparoscopy, dissection of adhesions and cholecystectomy", which immediately captured attention of the whole medical community [9]. By that time Erich Muhe had already performed 92 LCE surgeries [10]. The LCE operations of Mouret and Muhe differed in multiportality and the use of video monitors [11]. At the same time many ports increase postoperative pain, disrupt the aesthetics of the operation and increase the risk of complications such as hernias, wound infections, and hematomas [12]. Undoubtedly, any surgical intervention is a factor of aggression and injures body tissues due to the need to provide access to operative organs [13].

Since the beginning of the 21st century, surgery has undergone significant changes. The introduction and improvement of minimally invasive surgery has radically changed the idea of surgical trauma [14]. In the early 1990s LCE met all the standards of modern

medicine and gained worldwide recognition in clinical practice [15]. Thus, in 1992 the National Institutes of Health recognized it as a safe and effective treatment for almost all patients with gallstone disease [16].

Numerous advantages of laparoscopic surgery have now been proven, many of which are indicative in the treatment of any surgical pathology [17]. These advantages mainly include less surgical trauma, fewer postoperative complications (especially purulent-septic ones), a shorter recovery period, and a cosmetic effect [18].

LCE in Kazakhstan

The Aktobe Regional Children's Hospital based at the Department of Pediatric Surgery of the Aktobe State Medical Institute was the the first to perform endovideoscopic surgery in Kazakhstan under the supervision of Professor B.K. Dzhenalayev. Dr. V.I. Kotlobovsky paved the way in video laparoscopic operations in November 1991. He was the one to perform an appendectomy on a child. It is considered as the first laparoscopic operation on a child in the USSR.

The first videolaparoscopic cholecystectomy was performed by Academician M.A. Aliyev at the Scientific Center of Surgery named after Syzganov in May 1992. Subsequently, in 1994 a specialized department of endovideoscopic surgery was opened in the same center, where courses were organized for the training and advanced training of doctors in the field of endovideosurgery [19].

Optimal Timing for LCE

Based on the timing of the general pathogenesis, acute inflammation usually abates in 72 hours after the onset of inflammation and becomes chronic inflammation [20]. Therefore it is theoretically expected that all patients with acute cholecystitis will develop local and systemic inflammation within 72 hours of symptom onset, but local and systemic changes after this time may be unpredictable in different patients. The incidence of acute cholecystitis may decrease or may not improve, or even worsen, as is seen with delayed surgery. Therefore, it is assumed that cholecystectomy in the early stages of the disease can prevent the progression of cholecystitis during surgery, especially in severe complications associated with an increase in postoperative complications [21].

It may be considered that immediate cholecystectomy should be preferred over delayed cholecystectomy if possible within 72 hours of symptom onset. If symptoms persist for more than 72 hours at the time of surgery, then the timing of cholecystectomy should take into account other outcomes and risk factors [22].

Demand and interest in "scarless" surgery is currently undeniable, and minimally invasive surgical techniques represent a normal evolution. The benefits of less postoperative pain, fewer postoperative complications, and better cosmetic outcomes have been emphasized [23].

Usually laparoscopic cholecystectomy is recommended for patients with biliary-type symptoms or patients with complications of gallstone disease, as these patients are more likely to have recurrent and more severe symptoms.

Technical Aspects of Laparoscopic Cholecystectomy

Four ports are used in LCE: 10- or 12-mm umbilical port for the camera; 10 mm epigastric port, which is installed 4 cm below the xyphoid process, entering to the right of the sap-motor ligament; two 5 mm trocars placed along the midclavicular line above the umbilicus and anterior axillary line 4–5 cm below the costal margin, respectively (Figure 1) [23].

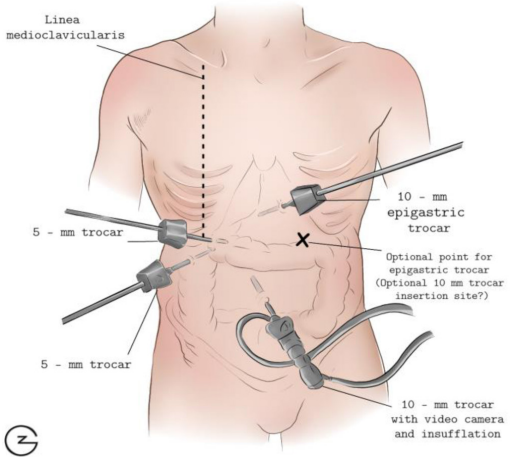

Figure 1 – Location of trocars or accesses

The operation is performed in the Trendelenburg position with the arms outstretched. An abdominal access is used when through the umbilicus a 10 mm casing is inserted which can be installed using a Hasson trocar or a Veress needle. The laparoscope must be inserted after insufflation of carbon dioxide up to 15 mm Hg with the abdominal cavity examined.

Based on data from clinical studies of the effect of pneumoperitoneal pressure reduction no difference observed in the average life expectancy of patients who underwent surgery with pressure ≤ 10 mm Hg and patients who were treated with a pressure of 10-15 mm Hg [24].

The patient is then placed in the reverse Trendelenburg position and tilted to the left to better visualize the gallbladder and surrounding structures.

Then under laparoscopic control two trocars are placed in the right hypochondrium and a 10-mm trocar in the epigastrium. Sometimes a fifth trocar is placed in the left hypochondrium for retraction, which makes it possible to better visualize the structures located in the hilum of the liver [25].

Traction of the gallbladder behind the fundus in the cranial direction and behind the neck to the right leads to tension of the cystic duct at a right angle to the common bile duct, thereby minimizing the chance of confusion between the 2 ducts (Fig. 2) [25].

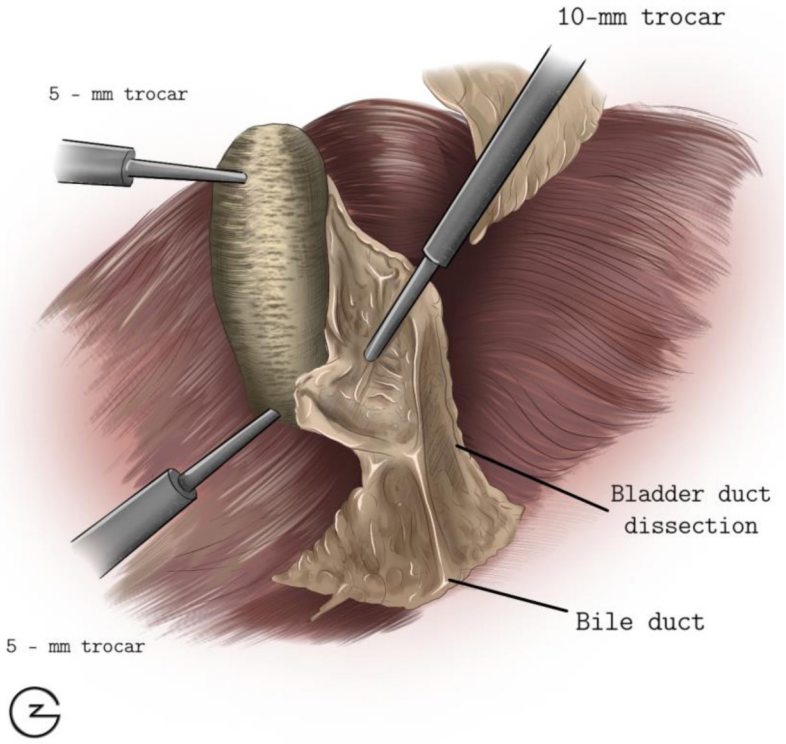

Figure 2 – Traction and gallbladder dissection technique

The right-to-left dissection is then started, the cystic duct is identified, and sufficiently mobilized to be accurately identified [25].

An important aspect of dissection is retraction of the gallbladder fundus in the cranial direction and traction of the neck downward and laterally. The gallbladder neck must be carefully mobilized to expose the junction of the gallbladder to the cystic duct. Then a “window” or a “hole” is created and the instrument is passed behind the cystic duct and artery demonstrating the absence of other formations in this zone going to the gallbladder or liver.

This is a required safety measure. The clip on the cystic duct is applied no earlier than the complete dissection of the Calot triangle and the instrument is passed behind the cystic artery and duct. If there is even a shadow of doubt, upfront surgery should be performed [25].

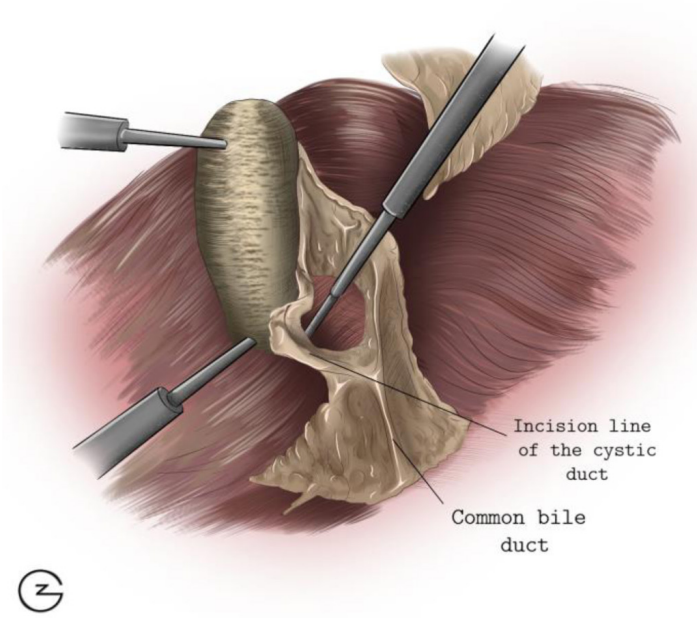

Figure 3 – Incision line of the cystic duct

Then, two clips are placed on the proximal portion of the cystic duct and cut with scissors (Fig 3).

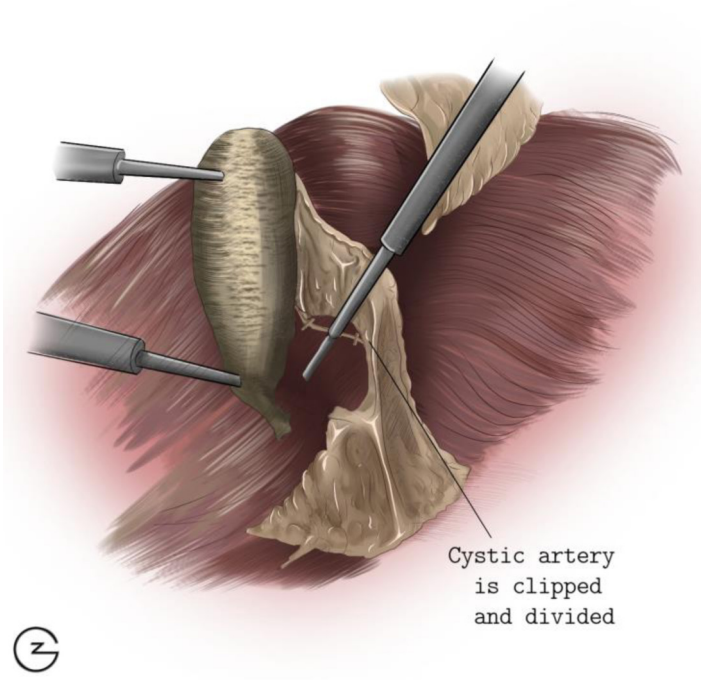

Figure 4 – Identification and dissection of the cystic artery

After transection the cystic duct, the dissection is continued to the left to expose the cystic artery. The cystic artery is transected after placing three clips (Fig. 4) [25].

The right and left transitional folds of the peritoneum are dissected using an electrocoagulator. When dissecting the transitional fold of the peritoneum, the gallbladder is separated from its hepatic bed using an electric knife with care so as not to miss the additional bile ducts entering the gallbladder directly from the hepatic bed. Small foci of bleeding are controlled by electrocoagulation [25].

Next, the gallbladder is raised above the edge of the liver. A plastic container is inserted into the abdominal cavity through the umbilical port, into which the gallbladder is placed. Then the container is closed and pulled out of the abdominal cavity (Fig. 5).

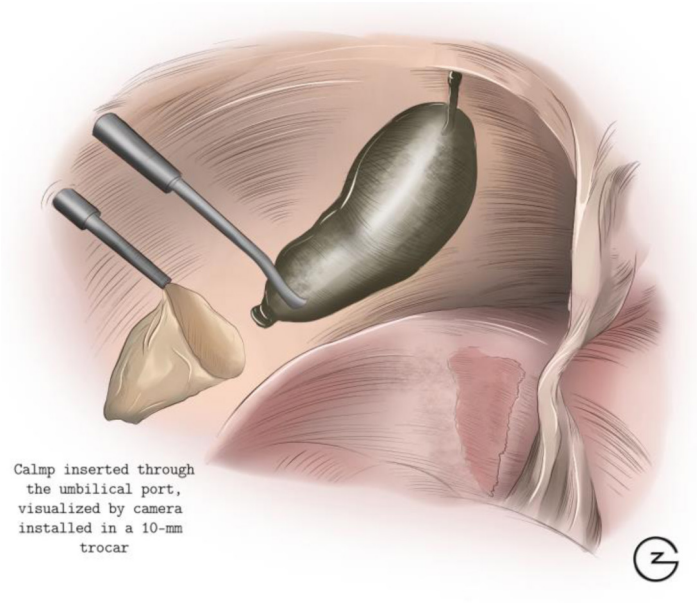

Figure 5 – The gallbladder is removed using a plastic bag.

In case of large stones, it may be necessary to expand the incision of the aponeurosis or remove stones from the container, which shall be carried out avoiding wound contamination [25].

Complications

Since laparoscopic cholecystectomy is the most frequently performed general surgical operation worldwide, this type of surgery correlates with an overall complication rate of 10% and is accompanied by a higher risk of biliary tract damage (0.1-1.5%) [26-28] than open cholecystectomy (0,1-0,2%) [26,29].

Factors predisposing to injury include anatomical features, pathology of the hepatobiliary tract, as well as incorrect identification of structures and the choice of incorrect tactics [30]. The most common cause of these lesions is due to misidentification of the common bile duct (CBD) or common hepatic duct (CHD) as a cystic duct or misidentification of the hepatic artery as a cystic artery [31].

Also the main problems leading to the development of complications include the lack of experience with the equipment, inability to perform cholangiography and a lack of understanding of electrosurgical principles. In addition, the cases may include "difficult gallbladder", which are associated with adhesions, obesity, inflammation or distension of the gallbladder and cirrhosis of the liver [32].

Considering the following factors: immediate morbidity, reduced quality of life and long-term survival, in addition to high mortality, which are associated with bile duct injury or biliary vascular injury, the strategy for safely performing LCE should not be underestimated [33]. Postoperative complications, especially life-long ones, significantly offset the benefits of a minimally invasive approach. Recent data suggest a downward trend in the incidence of bile duct injury (0.32%–0.52%) without a significant change in morbidity or mortality after LCE [29]. Based on this, it is important to understand that following a structured safe technical protocol helps to avoid injuries and negative outcomes of treatment.

Features of LCE in special groups of patients

Laparoscopic cholecystectomy has revolutionized the treatment of gallbladder pathologies. However, despite all the advantages of this method of treatment, the surgical community is reluctant to use it in relation to the elderly patients. Although laparoscopy is well established in the treatment of a wide range of gallbladder diseases, the conservative surgical trend suggests that the outcome of laparoscopic cholecystectomy in the geriatric patient pop-

ulation is not well defined [34]. However, age alone should not be a contraindication for laparoscopic cholecystectomy.

Some sources say that many elderly patients have complicated abdominal access for LCE due to comorbidities, complications and adhesive processes after previous surgical interventions. The operation can be more complicated and take longer, but laparoscopy is considered feasible in emergency cases, as it is a safe method. Care is required for both trocar triangulation and pneumoperitoneum induction [35].

Regarding the postoperative period, the safety of performing LCE in geriatric patients has been proven, but the risk of postoperative cardiovascular complications is slightly higher. To prevent these adverse events in the elderly, it is necessary to conduct a thorough preoperative preparation of the vascular, hemodynamic, and respiratory statuses.

The level of systemic inflammation and sepsis was one of the main factors influencing the poor outcome of LCE in the elderly. Among comorbidities, diabetes has been associated with both increased surgical and postoperative cardiovascular morbidity, and previous stroke and chronic renal failure are correlated with a high risk of cardiovascular complications.

With proper perioperative care, older people can benefit from a minimally invasive approach that reduces postoperative complications and shortens the length of hospital stay [36].

Acute cholecystitis is the second most common cause of acute abdomen during pregnancy. The main problems during laparoscopic operations in pregnant patients are as follows: material damage during the introduction of trocars due to improper technique (which is especially difficult in the third trimester due to the severity of the uterus) and a decrease in venous return to the patient during the procedure after the pneumoperitoneum is attached and compression of the inferior vena cava. Despite this, it has been found that the benefits of laparoscopic cholecystectomy are greater than open surgery in pregnant women. Benefits include less postoperative pain [37].

Most operations included in various reviews were performed in the second trimester, which many surgeons consider the safest for laparoscopic surgery. There is concern that laparoscopy in the first trimester may lead to spontaneous miscarriage, however, there is currently insufficient evidence to support this statement [38].

Thus, LCE may be safe to perform in pregnant women, but the indications for it should be carefully considered, and adequate preparation should be carried out in consultation with obstetricians and anesthesiologists [39].

In addition, there is concern about the safety of LCE in obese people. Based on a 2015 study, LCE can be performed safely and effectively in even highly obese patients with equally good results compared to patients with normal BMI. The frequency of intraoperative complications was low: from 1% to 2% in different BMI groups. The rates of postoperative complications in the BMI groups < 40 groups were higher than in the other two BMI groups, but the differences were not as statistically significant [40].

The degree of obesity of patients affected the time of surgery but had no relation to the outcome. Despite the increase in the time of surgery, bleeding volume, conversion rate, complications and length of hospital stay remained within the normal range. Therefore, LCE can also be safely performed in obese patients with the same efficacy as in patients with a BMI within the normal range [41].

Gallstone disease occurs in approximately 47% of patients with cirrhosis [42,43]. These patients are subject to higher morbidity [44] and mortality compared with patients without cirrhosis [45]

When surgery is required for patients with hepatic fibrosis and portal hypertension due to increased risks of complications, open cholecystectomy is preferred over laparoscopic cholecystectomy [46,47,48]

Portal inflow in cirrhosis of the liver decreases, due to which the flow of the hepatic artery increases, as a compensatory mechanism. Based on this, it is recommended to maintain intra-abdominal pressure at a minimum level and conduct exsufflation carefully, intermittently [47].

At present, based on numerous studies, LCE has become the option of choice in specific cases [44, 47, 49]. However, the laparoscopic approach has certain disadvantages in liver cirrhosis and requires special precautions.

Laparoscopic cholecystectomy is safe in patients with Child-Pugh A cirrhosis and should be used with caution in patients with Child-Pugh B cirrhosis given the high conversion ratio [1].

If a patient has cirrhosis with Child-Pugh class C or MELD score >13, laparoscopic surgery is not recommended. In that case alternative options can be used such as partial cholecystectomy [50] or endoscopic gallbladder drainage [51,52]. Endoscopic papillary balloon dilatation without sphincterotomy correlates with a low risk of bleeding but has limited efficacy for large stones [53] Endoscopic treatment with mechanical lithotripsy or sphincterotomy is recommended in case of larger stones [53]

Some studies have shown that severe fibrosis and anatomical abnormalities are more common in men, and therefore laparoscopic cholecystectomy is more

difficult in men than in women. This is because the differentiated action of sex hormones may play an important role in wound healing. The effect of exogenous administration of low and high doses of estradiol to rats was studied. It was found that low doses of estradiol inhibit the formation of connective tissue by 29%, whereas high doses inhibit it by 65%. It was concluded that estradiol prevents the formation of connective tissue in peritoneal injuries depending on a dose. It has been suggested that estrogen may inhibit macrophage activation or prevent their accumulation in the wound, thereby inhibiting adhesion development. This difference may explain the difficulty in gaining surgical access during LCE and the higher frequency of transition to open surgery in male patients [54].

In the early years, laparoscopic cholecystectomy was considered unsafe or technically difficult for acute cholecystitis [55]. Gaining more experience, it was clear thar the frequency of performing laparoscopic cholecystectomy for acute cholecystitis has increased, suggesting that it is technically feasible, but at the expense of a high conversion rate [56] and invasion of the common bile duct [57].

Routine open cholecystectomy may allow more patients to be operated on urgently. This is because most surgeons practice this particular method. But it is necessary to take into account the length of stay in the hospital and the impact on morbidity. In acute cholecystitis, laparoscopic cholecystectomy reduces postoperative morbidity, mortality, and the length of hospital stay [58]. Laparoscopic surgery also reduces the duration of operative time, the risk of developing pneumonia and wound infections [59].

Methods and Materials

We searched the PubMed, Embase, Scopus databases and the Cochrane Research Library for guidelines, articles reviewing the laparoscopic method of cholecystectomy. In addition, a manual search for publication was carried out in such reputable journals as Ann Surg, Lancet, BMJ, Brit J Surg, World J Gastroenterol, Surg Endosc, World J Surg, Am J Gastroenterol, Am J Surg, Langenbecks Arch Surg, Arch Surg, Chirurg, Jama Surgery. The search included such words as acute cholecystitis, acute calculous cholecystitis, cholelithiasis, gallstones, laparoscopic cholecystectomy.

Conclusion

Based on the review, it can be stated that the demand for and interest in “scarless” surgery is currently undeniable, and minimally invasive surgical methods represent a normal evolution. The benefits of less postoperative pain, fewer postoperative complications, and better cosmetic outcomes have been emphasized [21]. Carrying out LCE in the elderly, pregnant women and obese patients today does not cause big problems, the main thing is to take into account the characteristics of each patient. In the case of LCE in the elderly, careful preoperative preparation of the vascular, hemodynamic, and respiratory status should be carried out to prevent adverse events. And the optimal period for carrying out the safest laparoscopic surgical interventions in pregnant women is the second trimester. It is also necessary to remember that proper preparation should be carried out in consultation with obstetricians and anesthesiologists [38]. At the same time, LCE can be performed safely and effectively in even highly obese patients with equally good results compared to patients with normal BMI [40]. Laparoscopic cholecystectomy is safe in patients with Child-Pugh A cirrhosis and should be used with caution in patients with Child-Pugh B cirrhosis given the high conversion ratio [1]. If a patient has cirrhosis with Child-Pugh class C or MELD score >13, laparoscopic surgery is not recommended with alternative options to be offered such as partial cholecystectomy [50] or endoscopic gallbladder drainage [51,52]. Endoscopic papillary balloon dilatation without sphincterotomy is associated with a low risk of bleeding but has limited efficacy in case of large stones [53]. Endoscopic treatment with mechanical lithotripsy or sphincterotomy is recommended for larger stones [53].

References

1. Eugen Târcoveanu, Alin Vasilescu, Cristian Lupaşcu, Nutu Vlad, Marius Moraru, Carol Stanciu, Valentin Bejan, Costel Bradea. Laparoscopic Cholecystectomy in Cirrhotic Patients. 2020 Mar-Apr;115(2):213-219.

2. Gurusamy KS, Davidson C, Gluud C, Davidson BR. Early versus delayed laparoscopic cholecystectomy for people with acute cholecystitis. Cochrane Database Syst Rev. 2013;(6):CD005440.

3. Abbasova S.F. Laparoscopic cholecystectomy in patients of older age groups / S.F. Abbasova // Surgery. – 2011. – No.9. – pp. 83-85.

4. Kostyrnoi A.V., Kosenko A.V., Astapenko S.V., Baranovsky Yu.G. Prevention of intra-abdominal complications after operations on the stomach and duodenum / / Bulletin of emergency and restorative medicine. – 2012. – Volume 13, No. 2. – Pp. 290-293.

5. Michele Pisano, Niccolò Allievi, Kurinchi Gurusamy, Giuseppe Borzellino, Stefania Cimbanassi, Djamila Boerna; 2020 World Society of Emergency Surgery updated guidelines for the diagnosis and treatment of acute calculus cholecystitis, Nov. 2020

6. Shevchenko R.S. Features of Laparoscopic Cholecystectomy in patients previously operated on abdominal organs // Kharkov School of Surgery. – 2012. – No. 2. – Pp. 120-123.

7. Mortimore G., NICE Internal Clinical Guidelines team. 2014. Gallstone disease: diagnosis and management. Clinical guideline [CG188] https://www.nice.org.uk/guidance/cg188/chapter/1-Recommendations#managing-gallbladder-stones

8. Lyadov K.V., Egiev V.N., Ermakov N.A., Lyadov V.K., Markin A.Yu. Single Port Cholecystectomy. M.; Publishing House "Medpraktika-M"; 2012; 56.

9. Blum C.A., Adams D.B. Who did the first laparoscopic cholecystectomy? Journal of minimal access surgery. 2011; 7:165-168.

10. Remzi F.H., Kirat H.T., Kaouk J.H. et al. Single-port laparoscopy in colorectal surgery. Colorectal Dis. 2008;10(8):823-826.

11. Mouret P. How I developed laparoscopic cholecystectomy. Ann Acad Med Singapore. 1996; 25:744-747.

12. Lowry PS et al. Symptomatic port-site hernia associated with a non-bladed trocar after laparoscopic live-donor nephrectomy. J Endourol. 2003; 17:493-494.

13. Stolin A.V. Tactics of Treatment of Purulent-destructive Forms of Acute Calculous Cholecystitis. VolgGMU Bulletin. 2008; 4:28:34-36.

14. Bekhteva M.E., Baranov A.V., Panchenkov D.N. Surgery of a Single Laparoscopic Access: History and Current State of the Issue. Endoscopic surgery. 2012; 6:26-31.

15. Go Wakabayashi,Yukio Iwashita,Taizo Hibi,Tadahiro Takada,Steven M. Strasberg. Tokyo Guidelines 2018: surgical management of acute cholecystitis: safe steps in laparoscopic cholecystectomy for acute cholecystitis. doi.org/10.1002/jhbp.517

16. Hartwig W., Gluth A., Büchler M.W. Minimally invasive surgical therapy of acute cholecystitis. Chirurg. 2013;84(3):191-196.

17. Yu. G. Starkov, K. V. Shishin, I. Yu. Historical Aspects and Current State of Single Access Surgery. Surgery. 2012; 9:90-94.

18. Izimbergenov N.I., Karimova B.Zh., Koishibaev A.S., Izimbergenov M.N., Imanbaev K.S., Saduov M.A. Endovideoscopic surgery in Kazakhstan: current state and development prospects. 2016.

19. Bochsler P.N., Slauson D.O. Inflammation and repair of tissue. In: Slauson DO, Cooper BJ, editors. Mechanisms of disease: a textbook of comparative general pathology. 3rd ed. St. Louis: Mosby; 2002. p. 141.; Kumar V, Abbas AK, Fausto N. Chapter 2. In: Kumar V, Abbas AK, Fausto N, editors. Robbins and Cotran pathologic basis of disease. 7th ed: Elsevier Saunders; 2005. p. 47.

20. Borzellino G., Sauerland S., Minicozzi A.M., Verlato G., Pietrantonj C.D., Manzoni G., et al. Laparoscopic cholecystectomy for severe acute cholecystitis. A meta-analysis of results. Surg Endosc. 2008;22(1):8–15.

21. Borzellino G., Khuri S., Pisano M., Mansour S., Allievi N., Ansaloni L., Kluger Y. Timing of early laparoscopic cholecystectomy for acute calculous cholecystitis: a meta-analysis of randomized clinical trials | World Journal of Emergency Surgery 16 (2021)

22. Cotirlet A., Nedelcu M., Popa E., Anghel R., Rau S., Motoc I., Tincu E. Single Incision Laparoscopic Cholecystectomy. Chirurgia (2014) 109: 769-773 No. 6, November – December

23. Brendon J. Coventry, Upper Abdominal Surgery, Springer London Heidelberg New York Dordrecht 2014. DOI 10.1007/978-1-4471-5436-5

24. Jessica M. Ryan, Emer O'Connell, Ailín C. Rogers, Jan Sorensen and Deborah A. McNamara. Systematic review and meta-analysis of factors which reduce the length of stay associated with elective laparoscopic cholecystectomy, 2021. HPB (Oxford). 2021 Feb; 23(2): 161–172. Published online 2020 Sep 6. doi: 10.1016/j.hpb.2020.08.012.

25. Theodore N. Pappas, Aurora D. Prior, Michael S. Harnisch; translated from English under supervision of Prof. S.S. Harnas. Laparoscopic surgery. Atlas/. – M.: GEOTAR-Media, 2012 – 388 pages.

26. Berci G., Hunter J., Morgenstern L., Arregui M., Brunt M., Carroll B., Edye M., Fermelia D., Ferzli G., Greene F., Petelin J., Phillips E., Ponsky J., Sax H., Schwaitzberg S., Soper N., Swanstrom L., Traverso W. Laparoscopic cholecystectomy: first, do no harm; second, take care of bile duct stones. Surg Endosc. 2013; 27:1051–1054.

27. Fédération de chirurgie viscérale et digestive. Risk management to decrease bile duct injury associated with cholecystectomy: measures to improve patient safety. J Visc Surg. 2014; 151:241–244.

28. Barrett M., Asbun H.J., Chien H.L., Brunt L.M., Telem D.A. Bile duct injury and morbidity following cholecystectomy: a need for improvement. Surg Endosc. 2018;32:1683–1688.

29. Pucher P.H., Brunt L.M., Davies N., Linsk A., Munshi A., Rodriguez H.A., Fingerhut A., Fanelli R.D., Asbun H., Aggarwal R. SAGES Safe Cholecystectomy Task Force. Outcome trends and safety measures after 30 years of laparoscopic cholecystectomy: a systematic review and pooled data analysis. Surg Endosc. 2018; 32:2175–2183.

30. Callery M.P. Avoiding biliary injury during laparoscopic cholecystectomy: technical considerations. Surg Endosc. 2006; 20:1654–1658.

31. Iwashita Y, Hibi T, Ohyama T, Umezawa A, Takada T, Strasberg SM, Asbun HJ, Pitt HA, Han HS, Hwang TL, Suzuki K, Yoon YS, Choi IS, Yoon DS, Huang WS, Yoshida M, Wakabayashi G, Miura F, Okamoto K, Endo I, de Santibañes E, Giménez ME, Windsor JA, Garden OJ, Gouma DJ, Cherqui D, Belli G, Dervenis C, Deziel DJ, Jonas E, Jagannath P, Supe AN, Singh H, Liau KH, Chen XP, Chan ACW, Lau WY, Fan ST, Chen MF, Kim MH, Honda G, Sugioka A, Asai K, Wada K, Mori Y, Higuchi R, Misawa T, Watanabe M, Matsumura N, Rikiyama T, Sata N, Kano N, Tokumura H, Kimura T, Kitano S, Inomata M, Hirata K, Sumiyama Y, Inui K, Yamamoto M. Delphi consensus on bile duct injuries during laparoscopic cholecystectomy: an evolutionary cul-de-sac or the birth pangs of a new technical framework? J Hepatobiliary Pancreat Sci. 2017; 24:591–602.

32. Michele Pisano, Niccolò Allievi, Kurinchi Gurusamy, Giuseppe Borzellino, Stefania Cimbanassi, Djamila Boerna.World J Emerg Surg. 2020; 15: 61.Published online 2020 Nov 5. doi: 10.1186/s13017-020-00336-x. 2020 World Society of Emergency Surgery updated guidelines for the diagnosis and treatment of acute calculus cholecystitis.

33. Booij KAC, de Reuver PR, van Dieren S, van Delden OM, Rauws EA, Busch OR, van Gulik TM, Gouma DJ. Long-term Impact of Bile Duct Injury on Morbidity, Mortality, Quality of Life, and Work Related Limitations. Ann Surg. 2018; 268:143–150.

34. Stavros A Antoniou, George A Antoniou, Oliver O Koch, Rudolph Pointner, Frank A Granderath. Meta-analysis of laparoscopic vs open cholecystectomy in elderly patients. World J Gastroenterol. 2014 Dec 14; 20(46): 17626–17634. doi: 10.3748/wjg.v20.i46.17626.

35. Alessandra Surace, Silvia Marola, Rosa Benvenga, Alessandro Borello, Valentina Gentile, Alessia Ferrarese, Stefano Enrico, Valter Martino, Mario Nano, Mario Solej. Difficult abdominal access in laparoscopic cholecystectomy in elderly patients: our experience and literature review. Int J Surg. 2014;12 Suppl 2:S1-S3. doi: 10.1016/j.ijsu.2014.08.369.Epub 2014 Aug 23.

36. Dragos Serban, Bogdan Socea, Simona Andreea Balasescu, Cristinel Dumitru Badiu, Corneliu Tudor, Ana Maria Dascalu, Geta Vancea, Radu Iulian Spataru, Alexandru Dan Sabau, Dan Sabau, Ciprian Tanasescu. Safety of Laparoscopic Cholecystectomy for Acute Cholecystitis in the Elderly: A Multivariate Analysis of Risk Factors for Intra and Postoperative Complications. Medicina (Kaunas). 2021 Mar 2;57(3):230. doi: 10.3390/medicina57030230.

37. Edson R Marcos-Ramírez, Karla Guerra-Leza, Alejandra Téllez-Aguilera, Tomás E Benavides-Zavala, José R Fernández-Treviño, Gerardo Enrique Muñoz Maldonado. Laparoscopic cholecystectomy during pregnancy. Cir Cir. 2022;90(1):29-33. doi: 10.24875/CIRU.20001053.

38. Dimitrios Nasioudis, Diamantis Tsilimigras, Konstantinos P Economopoulos. Laparoscopic cholecystectomy during pregnancy: A systematic review of 590 patients. Int J Surg. 2016 Mar; 27:165-175. doi:10.1016/j.ijsu.2016.01.070. Epub 2016 Jan 28.

39. Takuma Iwai, Hiroshi Makino, Tadashi Yokoyama, Masahumi Yoshioka, Hiroshi Yoshida. Laparoscopic Cholecystectomy During Pregnancy: A Case Report and Review of Literature in Japan. Cureus. 2020 Apr 12;12(4): e7656. doi: 10.7759/cureus.7656.

40. Leong Tiong, Jaewook Oh. Safety and efficacy of a laparoscopic cholecystectomy in the morbid and super obese patients. HPB (Oxford). 2015 Jul;17(7):600-4. doi: 10.1111/hpb.12415. Epub 2015 Apr 23.

41. Yuta Enami, Takeshi Aoki, Kodai Tomioka, Tomoki Hakozaki, Takahito Hirai, Hideki Shibata, Kazuhiko Saito, Yojiro Takano, Junichi Seki, Sonoko Oae, Shoji Shimada, Kenta Nakahara, Yusuke Takehara, Shumpei Mukai, Naruhiko Sawada, Fumio Ishida, Masahiko Murakami, Shin-Ei Kudo. Obesity is not a risk factor for either mortality or complications after laparoscopic cholecystectomy for cholecystitis. Sci Rep. 2021 Jan 27;11(1):2384. doi: 10.1038/s41598-021-81963-5.

42. Elisa Cassinotti, Ludovica Baldari, Luigi Boni, Selman Uranues, Abe Fingerhut. Laparoscopic Cholecystectomy in the Cirrhotic: Review of Literature on Indications and Technique. DOI: 10.21614/chirurgia.115.2.208. PMID: 32369724.

43. Acalovschi M. Gallstones in patients with liver cirrhosis: Incidence, etiology, clinical and therapeutical aspects. World J Gastroenterol 2014; 20:7277-7285.

44. de Goede PJ, Klitsie SM, Hagen BJH, van Kempen S, Spronk HJ, Metselaar HJ, Lange JF, Kazemier G. Meta-analysis of laparoscopic versus open cholecystectomy for patients with liver cirrhosis and symptomatic cholecystolithiasis. Br J Surg. 2013; 100:209-216.

45. Hamad MA, Thabet M, Badawy A, Mourad F, Abdel-Salam M, Abdel-Rahman Mel-T et al. Laparoscopic versus open cholecystectomy in patients with liver cirrhosis: a prospective, randomized study. J Laparoendosc Adv Surg Tech A. 2010;20:405-409.

46. Delis S, Bakoyiannis A, Madariaga J, Bramis J, Tassopoulos N, Dervenis C. Laparoscopic cholecystectomy in cirrhotic patients: the value of MELD score and Child–Pugh classification in predicting outcome. Surg Endosc. 2010; 24:407-412.

47. Cobb WS, Heniford BT, Burns JM, Carbonell AM, Matthews BD, Kercher KW. Cirrhosis is not a contraindication to laparoscopic surgery. Surg Endosc. 2005; 19:418-423.

48. Cucinotta E, Lazzara S, Melita G. Laparoscopic cholecystectomy in cirrhotic patients. Surg Endosc. 2003; 17:1958-1960.

49. Puggioni A, Wong LL A Meta-analysis of laparoscopic cholecystectomy in patients with cirrhosis. J Am Coll Surg. 2003; 197:921-926.

50. Elshaer M, Gravante,G, Thomas K, Sorge R, Al-Hamali S, Ebdewi H Subtotal Cholecystectomy for "Difficult Gallbladders" Systematic Review and Meta-analysis. JAMA Surg. 2015; 150:159-168.

51. Gaglio PJ, Buniak B, Leevy CB Primary endoscopic retrograde cholecystoendoprosthesis: a nonsurgical modality for symptomatic cholelithiasis in cirrhotic patients. Gastrointest Endosc. 1996; 44:339-42

52. Pinheiro RH, Waisberg DR, Lai Q, Andraus W, Nacif LS, RochaSantos V, D'Albuquerque LAC Laparoscopic cholecystectomy and cirrhosis: patient selection and technical considerations Ann LAparsoc Endosc Surg. 2017;2:35-44.

53. Weinberg B, Shidy W, Lo S Endoscopic balloon sphincter dilation (sphincteroplasty) versus sphincterotomy for common bile duct stones. Cochrane Cochrane Systematic Review Version published: 18 October 2006.

54. Adem Akcakaya, Ismail Okan, Gurhan Bas, Gurol Sahin, Mustafa Sahin. Does the Difficulty of Laparoscopic Cholecystectomy Differ Between Genders Indian J Surg. 2015 Dec;77(Suppl 2):452-6. doi: 10.1007/s12262-013-0872-x. Epub 2013 Jan 31.

55. Rai R, Sinha A, Rai S: Randomized clinical trial of open versus laparoscopic cholecystectomy in the treatment of acute cholecystitis. Br J Surg. 2005, 92:44-49. Br J Surg. 2005;92:494-9.; Nuzzo G, Giuliante F, Persiani R: The risk of biliary ductal injury during laparoscopic cholecystectomy. J Chir (Paris). 2004,141:343-53.

56. Johansson M, Thune A, Nelvin L, Stiernstam M, Westman B, Lundell L: Randomized clinical trial of open versus laparoscopic cholecystectomy in the treatment of acute cholecystitis.; Br J Surg. 2005;92:44-9. 7. Asoglu O, Ozmen V, Karanlik H, Igci A, Kecer M, Parlak M, Unal ES: Does the complication rate increase in laparoscopic cholecystectomy for acute cholecystitis J Laparoendosc Adv Surg Tech. A 2004;14:81-6.

57. Johansson M, Thune A, Blomqvist A, Nelvin L, Lundell L: Management of acute cholecystitis in the laparoscopic era: results of a prospective, randomized clinical trial. J Gastrointest Surg. 2003; 7:642-5.

58. Chau CH, Tang CN, Siu WT, Ha JP, Li MK: Laparoscopic cholecystectomy versus open cholecystectomy in elderly patients with acute cholecystitis: retrospective study. Hong Kong Med J. 2002; 8:394-9.

59. Glavic Z, Begic L, Simlesa D, Rukavina A: Treatment of acute cholecystitis. A comparison of open vs laparoscopic cholecystectomy. Surg Endosc. 2001; 15:398- 401.

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