Research Article

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Implications of Hepatitis B and C on the Human Immunodeficiency Virus Infections

Hepatit B ve C'nin İnsan Bağışıklık Yetmezliği Virüsü Enfeksiyonları Üzerindeki Etkileri

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ABSTRACT

Objectives: Viral hepatitis and human immunodeficiency virus (HIV) infections are still significant causes of morbidity and mortality. This study investigatedaimed to investigate the effect of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection on HIV infection, investigate the epidemiological characteristics of co-infected patients and thus help identify risk factors for co-infection, evaluate the results and clinical information, and shape the treatment of patients.

Materials and Methods: This descriptive, cross-sectional study from January 2013 to July 2021 was conducted carried out on 758 patients, including 502 infected with HIV, 196 co-infected with HBV/HCV, and 60 co-infected with HCV/HIV. Comparison between groups in terms of categorical characteristics was analyzed with the Pearson chi-square test or Fisher-Freeman-Halton test. The changes in HIV infection in the presence of co-infections were examined with the multivariate multinomial logistic regression model.

Results: We found differences in our HIV-infected patients co-infected with HBV or HCV in gender, nationality, transmission routes, HIV viral load, and CD+4 T-cell count ($p<0.001$). There was no difference between the groups regarding age, opportunistic infection status, and malignancy status.

Conclusion: Our findings indicate that HBV and HCV may affect HIV infection infections. Our approach can focus on these points in co-infected patients, and we can effectively manage their treatment and follow-up.

Keywords: Human immunodeficiency virus, hepatitis B virus, hepatitis C virus, co-infection

ÖZ

Amaç: Viral hepatit ve insan bağışıklık yetmezlik virüsü (HIV) enfeksiyonları hala önemli morbidite ve mortalite nedenleridir. Bu çalışmada, hepatit B virüs (HBV) ve hepatit C virüs (HCV) enfeksiyonlarının HIV enfeksiyonu üzerindeki etkisinin araştırılması, ko-enfekte hastaların epidemiyolojik özelliklerinin ortaya çıkarılması ve böylece viral hepatit/HIV ko-enfeksiyonu için risk faktörlerinin belirlenmesi, sonuç ve klinik bilgilerin değerlendirilmesi ve hastaların tedavisinin şekillendirilmesine yardımcı olunması amaçlanmıştır.

Gereç ve Yöntemler: Ocak 2013'ten Temmuz 2021'e kadar olan bu tanımlayıcı, kesitsel çalışma, 502'si HIV ile enfekte, 196'sı HBV/HCV ile ko-enfekte ve 60'ı HCV/HIV ile ko-enfekte olmak üzere 758 hasta üzerinde gerçekleştirildi. Kategorik özellikler açısından gruplar arası karşılaştırma Pearson ki-kare testi veya Fisher-Freeman-Halton testi ile analiz edildi. Ko-enfeksiyon varlığında HIV enfeksiyonundaki değişiklikler çok değişkenli çok terimli lojistik regresyon modeli ile incelendi.

Bulgular: HBV veya HCV ile ko-enfekte HIV positiv hastalarda cinsiyet, ülke, bulaşma yolları, HIV viral yükü ve CD+4 T- hücre sayısında anlamlı farklılıklar bulduk ($p<0,001$). Gruplar arasında yaş, fırsatçı enfeksiyon ve malignite durumu açısından ise fark yoktu.

Sonuç: Bulgularımız HBV ve HCV'nin HIV enfeksiyonlarını etkileyebileceğini göstermektedir. Yaklaşımımıza göre HBV ve/veya HCV'nin HIV ko-enfeksiyonlarında, anlamlı noktalara odaklanarak tedavi ve takiplerinin etkin bir şekilde yönetilebilmesi mümkün olabilir.

Anahtar Kelimeler: İnsan bağışıklık yetmezlik virüsü, hepatit B virüs, hepatit C virüs, ko-enfeksiyon

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Introduction

Viral hepatitis and human immunodeficiency virus (HIV) infections are still significant causes of morbidity and mortality in vulnerable populations and developing countries (1). World Health Organisation (WHO) reports that hepatitis B virus (HBV) and hepatitis C virus (HCV) are responsible for 96% of hepatitis deaths and that deaths are due to chronic liver disease and liver cancer (2). An estimated 257 million people lived with chronic HBV infection and 71 million chronic HCV infections in 2016 (2). On the other hand, at the end of 2019, an estimated 38 million people lived with HIV (3). Co-infections with HBV and HCV are common in HIV-infected individuals due to the similarity of transmission routes. These infections' estimated prevalence varies by geographic region (4). Approximately 5-10% of HIV-positive patients are infected with HBV and 15-25% with HCV in various studies (5,6,7). In Turkey, an estimated 3,6 million people are infected with HBV, 800,000 people with HCV, and 25,000 people with HIV; also, HBV/HIV and HCV/HIV co-infection rates were 4,4% and 0,9%, respectively (8,9,10,11).

HIV accelerates liver disease progression in viral hepatitis; HIV hurts the natural course and progression of HBV infection. HBV/HIV co-infected individuals have a higher DNA replication rate and a lower spontaneous clearance rate (12). In addition, HIV accelerates cirrhosis, end-stage liver disease, hepatocellular cancer, and an increase in liver-related death rates with an increase in the rate of fibrous formation in the liver (13).

The rate of liver disease progression is increased in HCV/HIV co-infected individuals compared to individuals infected with HCV alone (14). Liver cirrhosis can occur in a shorter time in HIV-positive people co-infected with HCV than in HIV monoinfected ones (15). Comorbid conditions such as cardiovascular disease, cognitive impairments, kidney disease, osteoporosis, bone fractures, and diabetes are more common in HCV/HIV co-infected patients than HIV monoinfected patients (16,17). People with HBV/HIV infection, HCV/HIV infection, and HBV/HCV/HIV infection have higher mortality rates than people with any disorder alone (18,19,20).

It has been found that HIV has a significant effect on the course of HBV and HCV, but the opposite has not been shown reliably, and the impact of HBV and HCV on the natural history of HIV is controversial. This study aimed to investigate the effect of HBV and HCV infection on HIV infection, investigate the epidemiological characteristics of co-infected patients and thus help identify risk factors for co-infection, evaluate the results and clinical information, and shape the treatment of patients.

Materials and Methods

Study Population

This descriptive, cross-sectional study from January 2013 to July 2021 was carried out on 758 patients, including 502 infected with HIV, 196 co-infected with HBV/HCV, and 60 co-infected with HCV/HIV, in the Faculty of Medicine, Clinical Laboratory, PCR Unite of Kocaeli University and Department of Infectious Diseases and Clinical Microbiology of Health Science University, Antalya Training and Research Hospital in Turkey. Not all patients were treated; they were naive.

HBV and HCV were diagnosed by clinical standards of care and practice guidelines. Patients with positive hepatitis B surface antigen (HBsAg) and hepatitis C antibody (HCV Ab) were included in the study.

Ethics committee approval for this study was obtained from the Kocaeli University Clinical Studies Ethics Committee (approval number: KOU KAEK 201345).

Sampling

The plasma HIV-1 RNA detection and quantification levels samples from confirmed HIV-positive patients were measured using real-time-PCR (Abbott TagMan 2000, Illinois-Des Plaines USA) (lower limit as quantification, 10 IU/mL).

CD4+ T-cell counts were analyzed with BD Simultest™ CD4/CD8 (Becton, Dickinson, and Company BD Biosciences 2350 Qume Drive San Jose, CA 95131 USA).

HBsAg and HCV Ab measurements were determined using chemiluminescence immunoassays (Cobas e 601 analyzers, Roche Diagnostic, Mannheim, Germany).

Statistical Analysis

Descriptive statistics of the data obtained were calculated as the arithmetic mean, standard deviation, median value, first (25^{th}) and third quartile (75^{th}) (IQR: 75^{th}-25^{th}), absolute and relative frequencies, depending on the type and distribution of the features. The conformity of the numerical type features to the normal distribution was examined using the Shapiro-Wilks test. Since it was determined that numerical measurements did not show normal distribution, the Kruskal-Wallis test was used to compare the groups, and the post-hoc Dunn test determined the groups that differed. Comparison between groups in terms of categorical characteristics was analyzed with the Pearson chi-square test or Fisher-Freeman-Halton test. In addition, considering the univariate test results described above, the changes in HIV infection in the presence of co-infections were examined with the multivariate multinomial logistic regression model. The statistical significance level was accepted as $p<0.05$, and SPSS (v25) software was used for calculations.

Results

While the rate of men (66.7%) in the HIV + HCV group was significantly lower than only the HIV (86.8%) and HIV + HBV (90.8%) groups, the rate of women in the HIV + HCV group was considerably higher than the other two groups. The frequency of Turkish nationality (63.3%) in the HIV + HCV group was significantly lower than only HIV (96%) and HIV + HBV (93.9%). Baseline demographic, clinical, and laboratory characteristics of patients are shown in Table 1.

In the HIV + HCV group and HIV + HBV group, the frequency of those with homosexual transmission routes was significantly lower than in the HIV group. Still, the frequency of those with heterosexual transmission routes was considerably higher. In addition, the frequency of those with intravenous drug use (IVDU) route in the HIV + HCV group was significantly higher than in the other two groups.

The mean HIV-1 RNA load in the HIV + HBV group was significantly lower than in the other two groups ($p<0.001$). In the

Table 1. Baseline demographic and laboratory characteristics of the study patients

Characteristic			Patient with HIV-1 infection, (n=502) HIV + HCV, (n=60)	Patient with co-infection		p-value
				HIV + HBV, (n=196)	HIV + HCV, (n=60)	
Age, mean year (range)*	Mean		38 (18-80)	40 (18-77)	39 (18-77)	0.080
	SD		12,442	12,482	13,014	
	Percentiles	25	29.00	31.00	30.00	
		50	36.00	38.00	39.00	
		75	46.00	46.00	47.00	
Age group, n (%)[b]	18-24 25-29 30-39 40-49 >50		52 (10.4) 98 (19.5) 158 (31.5) 101 (20.1) 93 (18.5)	16 (8.2) 23 (11.7) 70 (35.7) 46 (23.5) 41 (20.9)	4 (6.7) 10 (16.7) 19 (31.7) 17 (28.3) 10 (16.7)	0.286
Gender, n (%)	Female Male		66 (13.2)[a] 435 (86.2)[a]	18 (9.2)[a] 178 (90.8)[a]	20 (33.3)[b] 40 (66.7)[b]	**<0.001**
Nationality, n (%)	Turkish Non-Turkish		482 (96.0)[a] 20 (4)[a]	184 (93.9)[a] 12 (6.1)[a]	38 (63.3)[b] 22 (36.7)[b]	**<0.001**
HIV transmission route, n (%)	Heterosexual Homosexual IVDU Unknown		253 (50.4)[a] 224 (44.6)[a] 2 (0.4)[a] 23 (4.6)[a]	122 (62.2)[b] 68 (34.7)[b] 1 (0.5)[a] 5 (2.6)[a]	36 (60.0)[b] 8 (13.3)[b] 14 (23.3)[a] 2 (3.3)[b]	**<0.001**
Baseline HIV-1 RNA load, mean copy/mL (range)*	Mean		2.2+E7 (0-1+E10)	1.2+E6 (8.5+E2-6.0+E7)	2.1+E6 (7.1+E8)	**<0.001**
	SD		4.4+E8	5.1+E6	12.8+E7	
	Percentiles	25	8.3+E3	2.9+E4	5.3+E3	
		50	4.6+E4	1.0+E5	7.6+E4	
		75	2.3+E5	6.5+E5	2.3+E5	
HIV-1 RNA load group, copy/ml, n (%)	<1+E5 1+E5-2+E5 2+E5-5+E5 >5+E5		313 (62.4)[a] 53 (10.6)[a] 53 (10.6)[a] 83 (16.5)[a]	95 (48.5)[b] 22 (11.2)[a] 25 (12.8)[a] 54 (27.6)[a]	32 (53.3)[ab] 12 (20.0)[b] 5 (8.3)[a] 11 (18.3)[ab]	**0.004**
Baseline CD4+ T cell count, mean cell/mm^3 (range)*	Mean		484 (0-1900)	363 (5-1659)	616 (0-1800)	**<0.001**
	SD		787,380	234,561	1658,820	
	Percentiles	25	237.00	220.75	123.25	
		50	378.00	356.00	242.00	
		75	588.25	476.50	506.50	
CD+4 T-cell count group, cell/mm^3	≤200 >200		103 (20.5)[a] 399 (79.5)[a]	48 (24.5)[ab] 148 (75.5)[ab]	20 (33.3)[b] 40 (66.7)[b]	**0.049**
Exist of sexually transmitted diseases, n (%)	None Exist		38.1 (75.9)[a] 12.1 (24.1)[a]	178 (90.8)[b] 18 (9.2)[b]	55 (91.7)[b] 5 (8.3)[b]	**<0.001**
Sexually transmitted diseases status, n (%)	HPV Leishmaniasis Syphilis Syphilis + HPV		13 (2.6)[a] 0 (0.0)[a] 107(21.3)[a] 1 (0.2)[a]	1 (0.5)[ab] 0 (0.0)[a] 17 (8.7)[b] 0 (0.0)[a]	0 (0.0)[b] 1 (1.7)[b] 4(6.7)[b] 0 (0.0)[a]	**<0.001**
Opportunistic infections status, n (%)[b]	TBC PCP CMV PML		13 (20.9) 4 (30.8) 5 (38.5) 4 (30.8) -	9 (4.6) 4 (30.8) 3 (33.3) - 2 (22.2)	2 (3.3) 1 (50.0) 1 (50.0) - -	0.390
Malignancy status, n (%)[b]			9 (1.8)	5 (2.6)	3 (5.0)	0.198

*Kruskal-Wallis test, [a]Pearson chi-square test, [b]Fisher-Freeman-Halton test, CMV: Cytomegalovirus, HBV: Hepatitis B, HCV: Hepatitis C, HIV: Human immunodeficiency virus, IVDU: Intravenous drug use route, PCP: Pneumocystis jiroveci pneomonia, PML: Progressive multifocal leukoencephalopathy, SD: Standart deviation, TBC: Mycobacterium tuberculosis, HPV: Human papillomavirus

HIV + HBV group, the frequency of those with HIV-RNA <1+E5 copies/mL was significantly lower than in the HIV group, but the other group differences were insignificant. In the HIV + HCV group, the frequency of HIV-RNA between 1+E5-2+E5 copies was significantly higher than in the other two groups (p=0.004). In the HIV + HBV group, the frequency of HIV-RNA loud >5+E5 documents was substantially higher than in the HIV group only (p=0.004).

There was a significant difference between HIV and HIV + HBV (p=0.003) and HIV + HCV (p=0.010) in CD4+ T-cell count. It was seen that the mean CD4+ T-cell count in the HIV + HBV group was significantly lower than in the other two groups. The rate of those with CD4 count ≤200 cells/mL in the HIV + HCV group was considerably higher than the group with only HIV, and the frequency of those with >200 cells/mL was significantly lower (p<0.001).

The frequency of other sexually transmitted co-infections in the HIV + HCV and HIV + HBV groups was significantly lower than in the HIV group. The source of this was syphilis infection (p<0.001).

HIV-1 RNA load and CD4 count were expressed as categorical, with a significant difference between the groups in both cases. However, there was no significant difference between the mean age and age distribution groups.

Significant results are defined above in Table 1. These are univariate test results, and the features found to be substantial were modeled together, and the comparison of the three groups was re-evaluated with the multivariate model. The results obtained are given in Table 2.

Comparing HIV + HBV vs. HIV, the incidence of HIV + HBV in men was significantly higher by 2,298 times (p=0.007). In addition, the frequency of HIV + HBV in those with other sexually transmitted co-infections was markedly lower by 0.313 times (p<0.001). Apart from this, no other difference was observed compared to HIV + HBV and HIV.

Comparing HIV + HCV vs. HIV, HIV + HCV frequency was found to be 2.773 times higher in those with HIV-1 RNA loads between 1.0+E5-2.0+E5 compared to those with HIV-1 RNA load <1.0+E5 (p=0.023). In addition, the frequency of HIV + HCV in "homosexual, heterosexual and unknown" transmission routes was significantly lower than those transmitted through IVDU (p<0,001). Apart from this, no other difference was observed compared to HIV + HCV and HIV.

Discussion

This is the first national study of HIV-HBV and HIV-HCV co-infected individuals characterizing HBV, HCV, and HIV parameters. This study analyses the effect of HBV and HCV infection on HIV infection. Characterizing HBV and HCV in HIV-infected patients advances our understanding of HBV and HCV in this setting to focus on HIV treatment efforts.

As epidemiological characters, there were significant changes in gender and nationality in our study. The number of women and non-Turkish individuals in HCV + HIV co-infected patients was higher than in the other two groups. In addition, in multivariate analysis, the number of men was more elevated in HBV + HIV patients. We found 63% of HCV + HIV co-infected patients from Central Asia and the Russian Federation (data not shown). In Central Asia, including Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, and Uzbekistan, the pooled mean prevalence of HCV infection was 13.5% [95% confidence interval (CI): 10.9-16.4%] among non-specific clinical populations and 51.3% (95% CI: 46.9-55.6%) among people who inject drugs (21). Since their independence from the Soviet Union, public health and healthcare infrastructure have deteriorated in these countries, resulting in a re-emergence of infectious diseases, making it the region with one of the highest HCV prevalence levels worldwide (22,23,24). In our study, 23.3% of 60 HCV + HIV patients were IVDUs, taller and more significant

Table 2. Multivariate analysis of factors affecting HBV and HCV infection in HIV-infected people

			Patient with coinfection					
			HIV + HBV			**HIV + HCV**		
Variable	**Risk**	**Reference**	**OR**	**p-value**	**95% CI**	**OR**	**p**	**95% CI**
Nationality	Turkish	Non-Turkish	0.511	0.102	0,228-1,142	0.144	**0.001**	0.059-0.351
Gender	Male	Women	2,298	0.007	1,251-4,224	0.791	0.569	0.353-1,772
Presence of malignancy	Exist	None	1,313	0.642	0.416-4,145	3.446	0.095	0.807-14,713
HIV-1 RNA load, copies/mL	1.0+E5-2.0+E5	<1.0+E5	1,572	0.121	0.888-2,781	2.773	**0.023**	1,152-6,673
	2.0+E5-5.0+E5	<1.0+E5	1,535	0.132	0.879-2,680	0.891	0.844	0.282-2,814
	>5.0+E5	<1.0+E5	2,131	0.001	1,371-3,313	1.461	0.399	0.605-3,531
CD4+ T-cell count, cells/mm^3	>200	≤200	1,098	0.666	0.717-1,682	0.708	0.349	0.343-1,460
Presence of coinfection	Exist	None	0.313	**0.001**	0.183-0,537	0.383	0.096	0.124-1,187
HIV-1 transmission route	MSM	IVDU	0.762	0.828	0.066-8,750	0.010	**0.001**	0.002-0.057
	Heterosexual	IVDU	1,212	0.877	0.106-13,805	0.026	**0.001**	0.005-0.131
	Unknown	IVDU	0.486	0.588	0.036-6,632	0.018	**0.001**	0.002-0.157
	Intercept	-	-	0.367	-	-	**0.001**	-

CI: Confidence interval, p: p-value, OR: Odds ratio, MSM: Men who have sex with men, HBV: Hepatitis B virus, HCV: Hepatitis C virus, HIV: Human immunodeficiency virus

than the other two groups (p<0.001). The route of homosexual transmission was more elevated in HIV monoinfected patients than the others. WHO estimated that 52% of the 15.6 million global PWID have evidence of hepatitis C exposure (25). In Central Asia, the number of PWID is higher (26). Viral hepatitis is not circulating in the homosexual community, so it may follow individuals carefully in Turkey.

We found that HIV-infected men were more affected by HBV than HCV women. In some studies, similar results were reported (27,28,29). Interestingly, both HCV and HIV mono-infected individuals generally predominate in the male population (30,31,32). On the other hand, there are conflicting reports regarding the high incidence of infection in male or female individuals. This is not apparent but may be due to different methodological methods or epidemiological differences in study populations. Higher incidence in males than females in HIV-positive patients co-infected with HBV or HCV; may be related to problems where men are more likely to develop risky behaviors and men have higher rates of homosexuality and injecting drug use than women (33,34). According to age groups, there was no difference between the three groups in this study. However, it was observed that the prevalence increased with age in all three groups and peaked in the groups, especially in the 30-39 age range. These findings concord with those reported previously (35,36,37). This may be because younger patients are more exposed to risky behaviors than older patients.

In our study, HIV-1 RNA load was higher in HBV/HIV co-infected patients. HIV infection adversely affects all stages of the natural history of hepatitis B, leading to increased persistent infection rates, higher HBV-DNA levels, lower rates of hepatitis B e antigen loss, and increased liver-related complications and death rates at low CD+4 T-cell counts (38). Whether HBV infection does affect HIV infection is not well known. Before the general availability of highly active antiretroviral therapy, clinical studies evaluating the impact of HBV on HIV progression have shown inconsistent results (39,40). Some studies have found no difference in HIV progression between those with and without chronic HBV (41,42). It has been suggested that a persistent immune activation state may upregulate HIV replication in patients with chronic HBV infection (41,42). Patients co-infected with HIV/HBV have been shown to have a 3.6 - to 6.8 - fold risk of progression to AIDS in early prospective cohort studies compared to those without co-infection (39,43). In the Swiss HIV Cohort Study; the negative impact of HBV on HIV has been demonstrated: It has been shown that HBsAg-positive patients have significantly impaired CD4+ T-cell recovery in the first three years of antiretroviral treatment compared to HIV-positive patients without HBV infection, despite similar virological efficacy of antiretroviral therapy (44). A recent study has observed that anti-HBc in HBV + HIV co-infected patients hurts the CD4/CD8 ratio increase. In the subset of patients with low immune status, a significant increase in CD8+ T-cell counts was also demonstrated up to 24 months after initiating effective antiretroviral therapy (45). We also found an immunological difference in HBV/HIV co-infected patients; the immunological effect of HBV on HIV should be kept in mind in planning the treatment of HIV patients co-infected with HBV and in the follow-up of these patients.

In the subgroup analysis, the number of HCV + HIV co-infected patients was higher than the CD4+ T-cell count of ≤200 cells/mm^3. Chun et al. (46) had found that untreated HIV-positive patients with and without anti-HCV antibodies at the time of HIV diagnosis had an increased risk of AIDS or death to a similar extent. Similar results had been shown in the other studies (47,48,49). In one study, a higher CD4+ T-cell count (>200 cells/μL) was associated with a reduced risk of HIV-positive patient co-infection with HCV or HBV (50). In that study, increased differentiation was observed in CD4+ Th17 effector cells in HCV-infected hepatocytes. It was stated that this might cause HCV negatives to have higher CD4+ T-cell counts than positives. Although there have been different immunological results in HCV + HIV co-infected patients, this may lead to the hypothesis that treating HCV during the treatment of these patients will result in immunological recovery by increasing the CD4+ T-cell count.

We found that the frequency of syphilis co-infection was higher in the HIV monoinfected group than in the other two groups. This can be interpreted as HBV and HCV in HIV-infected patients reducing the risk of a second co-infection. Virus-virus interactions strongly influence co-infection; in the most comprehensive superinfection exclusion test to date, prophage arrays reduced culture co-infection by other prophages and had a weaker effect on extrachromosomal virus co-infection (51). The presence of viral co-infections minimizes the risk of bacterial co-infection. The relationship between HIV and syphilis can be explained by behavioral factors and genital ulceration facilitating HIV transmission in syphilis patients (52). HIV syphilis co-infection rates vary between 8-25% (53,54,55). HIV serology in syphilis patients and syphilis serology in HIV patients should be screened. In HIV-positive patients co-infected with HBV and HCV, syphilis screening should be performed, although syphilis was found less common in our study.

Conclusion

We found differences in our HIV-infected patients co-infected with HBV or HCV in gender, nationality, transmission routes, HIV viral load, and CD+4 T-cell count. Our findings may indicate that HBV and HCV may affect HIV infections. Our approach can focus on these points in co-infected patients, and we can effectively manage their treatment and follow-up.

Ethics

Ethics Committee Approval: Ethics committee approval for this study was obtained from the Kocaeli University Clinical Studies Ethics Committee (approval number: KOU KAEK 201345).

Informed Consent: Patients' informed consent couldn't be required due to the study's retrospective design.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.S.Y., M.S., Concept: F.S.Y., M.S., Design: F.S.Y., M.S., Data Collection or Processing: M.S., Analysis or Interpretation: F.S.Y., M.S., Literature Search: F.S.Y., Writing: F.S.Y.

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