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ABSTRACT

The first pandemic wave of coronavirus disease 2019 (COVID-19) induced a considerable increase in several antivirals and antibiotics in surface water. The common symptoms of COVID-19 are viral and bacterial infections, while comorbidities (e.g., hypertension and diabetes) and mental shock (e.g., insomnia and anxiety) are nonnegligible. Nevertheless, little is known about the long-term impacts of comorbidities and mental shock on organic micropollutants (OMPs) in surface waters. Herein, we monitored 114 OMPs in surface water and wastewater treatment plants (WWTPs) in Wuhan, China, between 2019 and 2021. The pandemic-induced OMP pollution in surface water was confirmed by significant increases in 26 OMP concentrations. Significant increases in four antihypertensives and one diabetic drug suggest that the treatment of comorbidities may induce OMP pollution. Notably, cotinine (a metabolite of nicotine) increased 155 times to 187 $ng\cdot L^{-1}$, which might be associated with increased smoking. Additionally, the increases in zolpidem and sulpiride might be the result of worsened insomnia and depression. Hence, it is reasonable to note that mental-health protecting drugs/behavior also contributed to OMP pollution. Among the observed OMPs, telmisartan, lopinavir, and ritonavir were associated with significantly higher ecological risks because of their limited WWTP-removal rate and high ecotoxicity. This study provides new insights into the effects of comorbidities and mental shock on OMPs in surface water during a pandemic and highlights the need to monitor the fate of related pharmaceuticals in the aquatic environment and to improve their removal efficiencies in WWTPs.

1. Introduction

The first case of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was reported in Wuhan, China, in December 2019 [1], and by April 2020, 50 333 cases had been confirmed in Wuhan, including 9689 severe cases and 3869 mortalities. Wuhan experienced the first pandemic wave of COVID-19, which was declared a public health emergency of international concern by the World Health Organization on 30 January 2020 [2]. The transmission, variants, and effective drugs for SARS-CoV-2 are the most urgent issues to be studied [3–5], and the environmental impact of the COVID-19 pandemic has also attracted increasing attention [6–9]. To contain the spread of SARS-CoV-2, Wuhan was placed under lockdown for 76 days from 23 January 2020 to 8 April 2020. The lockdown of the city led to a significant reduction in human and industrial activities, which improved air quality (e.g., particulate matter with an aerodynamic diameter of 2.5 μm or less and NO_2) and water quality (e.g., ammonium nitrogen (NH_4^+-N), chemical oxygen demand and dissolved oxygen) [7,8]. In contrast, an increased load of organic micropollutants (OMPs) in surface waters was expected

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and confirmed by some studies [6,9], which could be related to pharmaceutical applications during the COVID-19 pandemic wave [10–12].

Early attention was focused on 11 antiviral drugs using quantitative structure–activity relationship modeling. Kuroda et al. [13] predicted that conventional wastewater treatment plants (WWTPs) would be inefficient in eliminating six antivirals (e.g., remdesivir and ribavirin); eight antivirals (e.g., lopinavir, ritonavir, remdesivir, and ribavirin) could lead to a high/moderate ecotoxicological risk in receiving river waters. Some field studies have been conducted to investigate the impact of the COVID-19 pandemic wave on OMP contamination in surface waters [6,9]. Chen et al. [6] analyzed 72 drugs (the antiviral drug ribavirin, 31 antibiotics, and 40 glucocorticoids) in surface waters in Wuhan eight weeks and five months after the lockdown was lifted and found a higher occurrence of ribavirin and azithromycin than in previous reports and the potential risks of sulfamethoxazole and azithromycin to aquatic organisms. Zhang et al. [9] analyzed three antivirals (i.e., lopinavir, ritonavir, and chloroquine) in the surface waters of Wuhan at two weeks, three months, and eight months after the lifting of the lockdown and found that the COVID-19 pandemic may have increased the concentrations and ecological risks of lopinavir and ritonavir in surface waters. As expected, antivirals (ribavirin, lopinavir, and ritonavir) and antibiotics (azithromycin and sulfamethoxazole) were observed with increased concentrations or ecological risks in surface waters during the COVID-19 pandemic. Seasonal variation is an important factor influencing the concentration of OMPs (especially pharmaceuticals) in surface waters [14,15]. Therefore, using OMP data in the same season (e.g., May 2021) as a reference to attribute increased OMP contamination to the COVID-19 pandemic.

A large body of literature strongly suggests that the impact of the COVID-19 pandemic on OMPs in surface waters is not limited to antivirals and antibiotics. The pandemic wave of COVID-19 has caused both physical damage and psychological shock to the public [16–18]. The most well-known and prevalent physical damage for COVID-19 patients is viral infection (SARS-CoV-2) and bacterial coinfection [10,12,19]. Additionally, the comorbidities of COVID-19 patients are nonnegligible [20,21]. A retrospective cohort study in Wuhan, China, included 191 COVID-19 patients (54 died in hospital), of whom 91 (48%) patients had a comorbidity, with hypertension being the most common (30% of patients), followed by diabetes (19% of patients) and coronary heart disease (8% of patients) [18]. As a result, the contamination of surface waters by cardiovascular drugs needs to be monitored, while the variations in drugs used to treat comorbidities (i.e., drugs other than antivirals and antibiotics) have rarely been studied. In addition, the pandemic wave of COVID-19 caused a great psychological shock to the public, not only limited to COVID-19 patients and frontline health workers but also to the uninfected population [22,23]. Psychotropic drugs for anxiety and insomnia can be used to reduce and eliminate the adverse effects of psychological shock. However, few studies have linked psychotropic drugs in surface waters to the COVID-19 pandemic wave. A better understanding of the relationship between the COVID-19 pandemic wave and OMP contamination is helpful in mitigating the adverse effects of a similar epidemic on surface waters in the future.

Accordingly, in this study, the concentrations of multiple classes of OMPs (e.g., antivirals, antibiotics, cardiovascular drugs, and psychiatric drugs) potentially affected by the COVID-19 pandemic were measured in typical Wuhan surface waters in December 2019 (the beginning of the COVID-19 pandemic), May 2020 (after the first COVID-19 pandemic wave), and May 2021 (one year after the first COVID-19 pandemic wave); moreover, their fate in WWTPs and their ecological risks in surface waters were assessed. This work provides a better understanding of the COVID-19 pandemic and OMPs in surface waters and suggests potential strategies to mitigate the adverse effects of the epidemic on OMP contamination of surface waters.

2. Materials and methods

2.1. Chemicals

In this study, 114 OMPs were selected based on the clinical documentation of medication use in COVID-19 patients (i.e., physical damage: viral and bacterial infections (6 antivirals and 42 antibiotics), comorbidities (11 cardiovascular drugs); mental shock: insomnia and anxiety (14 psychiatric drugs)), prescription frequency, sales data, and environmental priority [6,12,18,24–26]. Detailed information on these OMPs is provided in Table S1 in Appendix A. The selected OMPs (with $\geq$ 95% powder purity or 100 mg·mL^{-1} solution purity) were purchased from First Standard (China) or Sigma-Aldrich (Canada) and stored at −20 °C. The 22 internal standards (100 μg·mL^{-1} concentration) listed in Table S1 were purchased from First Standard and stored at −20 °C. Methanol (99.9% purity; Thermo Fisher Scientific, USA) and acetonitrile (99.9% purity; Thermo Fisher Scientific) were used as the solvent and mobile phases, respectively, for OMPs during liquid chromatography. Oasis HLB (6 cubic centimeter, 500 mg) solid phase extraction (SPE) cartridges were purchased from Waters (USA).

2.2. Study site and sample collection

Wuhan (8569 km^2), with a population of approximately 13.65 million, is the capital of Hubei Province, China. It is located in the middle reaches of the Yangtze River. In total, 14 sampling sites (Fig. S1(a) in Appendix A) were selected in the Yangtze River (11 points marked as Y1, Y2,..., Y11) and the Hanjiang River (three points marked as H1, H2, and H3). Additionally, seven sampling sites were selected in Nanhu Lake (marked as N1, N2,..., N7) (Fig. S1(b) in Appendix A), which is the third largest urban lake in Wuhan. Jinyintan Hospital in Wuhan was one of the first hospitals to receive COVID-19 patients. Accordingly, two WWTPs (A and B) in the vicinity of this hospital were selected to assess the occurrence of OMP in the influent and effluent of the WWTPs and to determine the OMP removal efficiencies of the WWTPs. Water samples were collected from the Yangtze and Hanhu River three times, in December 2019 (the start of the COVID-19 pandemic), May 2020 (after the first COVID-19 pandemic wave) and May 2021 (one year after the first COVID-19 pandemic wave). The discharge rates of the Yangtze and Hanjiang rivers during the three sampling periods were 10 500 and 667 m^3·s^{-1}, 17 900 and 1200 m^3·s^{-1}, and 29 500 and 1670 m^3·s^{-1}, respectively. The daily wastewater treatment capacities of WWTPs A and B in May 2020 and May 2021 were 630 000, 510 000, 580 000, and 540 000 t·d^{-1}, respectively. As the water level data for Nanhu Lake were not available for two years, it was assumed that the water level change during this period was small. Water samples from Nanhu Lake (seven designated sampling sites) and two WWTPs (influent and effluent) were collected twice (May 2020 and May 2021). The water quality parameters in the influent and effluent of the WWTPs are presented in Table S2 in Appendix A. A total of 77 water samples were collected over a period of 18 months.

2.3. Sample pretreatment and OMP analysis

The collected water samples were preprocessed from 500 to 0.5 mL by SPE using oasis HLB cartridges. Subsequently, the samples were passed through 0.7 μm glass fiber filter membranes, 0.25 g disodium ethylenediaminetetraacetate was added, the pH was adjusted to lower or equal to 3 with 3 mol·L^{-1} HCl, and 100 μL of 22 mixed internal standards (100 μg·L^{-1} of each) was added. The SPE procedures were adopted from the method of Ref. [27].

The 114 OMPs were analyzed using a hybrid triple quadrupole ion trap mass spectrometer system (QTRAP 5500 LC-MS/MS; AB SCIEX, USA) equipped with an electrospray ion source and coupled to an EXION LC™ AD (AB SCIEX). Furthermore, a Phenomenex analytical column (Kinetex 2.6 μm F5 100A; 50 mm × 3.0 mm; USA) was also used for liquid chromatographic separation, with the column temperature maintained at 40 °C and a 14 minute gradient elution used; in addition, Phase X contained 0.1% (v/v) high performance liquid chromatography (HPLC) grade formic acid in Milli-Q water, and Phase Y was HPLC grade acetonitrile. The liquid phase method was performed, and the mass spectrometry (MS) parameters were set according to the method of Ref. [27]. The injection volume was 5 μL. The MS/MS parameters of the 114 OMPs and 22 internal standards are provided in Table S1. Multi-Quant software (version 2.0.2, AB SCIEX) was used for data processing. The recovery of eight OMPs (5 OMPs: 17%–38%; 3 OMPs: > 150%) showed acceptable stability and repeatability, while the remaining 106 OMPs showed favorable recoveries (47%–143%) (Table S3 in Appendix A).

2.4. Ecological risk assessments

The potential ecological risk of individual OMPs in the surface water was calculated based on the risk quotient (RQ) as follows:

$$\mathrm{RQ} = \mathrm{MEC}/\mathrm{PNEC} \quad (1)$$

where MEC is the measured concentration of OMPs in the surface water and PNEC is the predicted no-effect concentration of OMPs. The PNEC value was calculated from the ratio of the toxicity test data to the corresponding assessment factor (AF) as follows [28,29]:

$$\mathrm{PNEC} = \frac{\mathrm{EC}_{50}\ \text{or}\ \mathrm{LC}_{50}}{\mathrm{AF}} \quad (2)$$

The half maximal effective concentration (EC_{50}) and median lethal concentration (LC_{50}) values for individual OMPs were obtained from ECOSAR (version 2.2) developed by the Office of Chemical Safety and Pollution Prevention of the US Environmental Protection Agency or from Ref. [9] and are presented in Table S4 in Appendix A. The AF value was 1000 for acute toxicity. Moreover, the RQ ranking criteria were as follows: RQ ≥ 1, high risk; 0.1 ≤ RQ < 1, medium risk; 0.01 ≤ RQ < 0.1, low risk; and RQ < 0.01, marginal risk [30,31].

3. Results and discussion

3.1. OMP occurrence in surface water

Based on the OMP data acquired in May 2021, 33 OMPs were detected in all water samples of the Hanjiang River, Yangtze River, and Nanhu Lake. These included beta blocker intermediate (atenolol acid), eight antibiotics (three macrolides and five sulfonamides), antipyretic analgesic (phenazone), four antivirals (arbidol, lamivudine, lopinavir, and ritonavir), five cardiovascular drugs (diltiazem, irbesartan, lidocaine, telmisartan, and valsartan), three doping agents (1,7-dimethylxanthine, caffeine, and cotinine), five insecticides (2,3,5-trimethacarb, carbofuran, fenobucarb, isoprocarb, and propoxur), four psychiatric drugs (carbamazepine, diazepam, diphenhydramine, and sulpiride) and two wide-spectrum antibiotics (climbazole and fluconazole). Doping (44%–62%), atenolol acid (16%–29%, due to high detection levels, atenolol acid was classified separately), and cardiovascular drugs (11%–18%) were the top three OMPs among the total OMPs in Nanhu Lake, while doping (36%–71%), sulfonamides (6%–25%), and atenolol acid (6%–11%) were dominant in the Hanjiang and Yangtze Rivers (Fig. 1(a)). Thus, although the OMP composition differed between the rivers and the lake, it was similar between the two rivers. The catalogs of OMPs detected in the rivers and the lake were highly consistent, suggesting that OMP pollution is widespread in these two types of water bodies. Furthermore, the presence of antibiotics, cardiovascular drugs, psychiatric drugs, doping, and insecticides was consistent with those reported in previous surface water studies [24,32,33]. The four antivirals detected (arbidol, lamivudine, lopinavir, and ritonavir) suggest that the issue of antiviral contamination of surface waters needs to be urgently addressed.

The concentration of each detected OMP ranged from the not detected level to 1187 ng·L^{-1} (1,7-dimethylxanthine in Nanhu Lake) (Fig. 1(b)), which was consistent with other studies conducted worldwide on surface water OMPs [34,35]. Caffeine (154 ng·L^{-1}) was the OMP with the highest concentration in the Yangtze River, but this concentration was lower than that previously reported in the lower reaches of the Yangtze River (Nanjing: 786 ng·L^{-1} and Shanghai: 824 ng·L^{-1}) [36], which could be due to the cumulative effect of caffeine from upstream to downstream. In addition, 1,7-dimethylxanthine, which has been shown to be a major metabolite of caffeine [37], had the second highest concentration (67 ng·L^{-1}). The combined presence of caffeine and 1,7-dimethylxanthine suggests high caffeine pollution in the Yangtze River. Atenolol acid (28 ng·L^{-1}), which is the main metabolite of atenolol and metoprolol and showed refractory biodegradability, ranked third [38]. This was followed by lincomycin (22 ng·L^{-1}), cotinine (21 ng·L^{-1}), and carbofuran (21 ng·L^{-1}). The top six OMPs in the Hanjiang River were caffeine (68 ng·L^{-1}), 1,7-dimethylxanthine (51 ng·L^{-1}), carbofuran (51 ng·L^{-1}), sulfaclozine (46 ng·L^{-1}), lincomycin (37 ng·L^{-1}), and atenolol acid (34 ng·L^{-1}), while in Nanhu Lake, they were 1,7-dimethylxanthine (1187 ng·L^{-1}), atenolol acid (326 ng·L^{-1}), telmisartan (111 ng·L^{-1}), caffeine (57 ng·L^{-1}), climbazole (50 ng·L^{-1}), and irbesartan (46 ng·L^{-1}). Among them, two OMP metabolites (atenolol acid and 1,7-dimethylxanthine) were detected in the Yangtze River, Hanjiang River, and Nanhu lake, suggesting that more attention should be given to the concentration and ecological risks of OMP metabolites in surface water. Overall, the total concentration range of the 33 OMPs detected was 323–359 ng·L^{-1} (median: 355 ng·L^{-1}) in the Hanjiang River, 237–328 ng·L^{-1} (median: 271 ng·L^{-1}) in the Yangtze River, and 736–1946 ng·L^{-1} (median: 896 ng·L^{-1}) in Nanhu Lake. The order of OMP pollution levels was Nanhu Lake > Hanjiang River > Yangtze River, which may be due to the level of flow, flow rate, and contribution of WWTP effluent. Although the results indicate that the rivers were less threatened by OMP metabolites, the overall threats remain because OMPs can be transferred downstream or to the ocean. Therefore, measures need to be taken to effectively control OMP pollution from their sources and water treatment processes.

3.2. Effect of COVID-19 on OMP occurrence

Among the three sampling periods, seven OMPs (zolpidem, ribavirin, azithromycin, remdesivir, sulfaclozine, gliclazide, and roxithromycin) were detected only in May 2020 (Fig. 2(a)), suggesting that the COVID-19 pandemic may have resulted in new OMPs in the Yangtze River (Y6–Y11) (Fig. S1 in Appendix A). The concentrations of 16 OMPs, namely, two antivirals (lopinavir and ritonavir), two antibiotics (clarithromycin and lincomycin), three antihypertensives (telmisartan, valsartan, and irbesartan), three doping agents (cotinine, caffeine, and 1,7-dimethylxanthine), and 6 other drugs (lidocaine, bisacodyl, primidone, phenazone, naproxen, and sulpiride), were significantly higher (T test, $p < 0.05$) in May 2020 than in December 2019 (Fig. 2(b)). In addition, the concentrations of the 16 OMPs

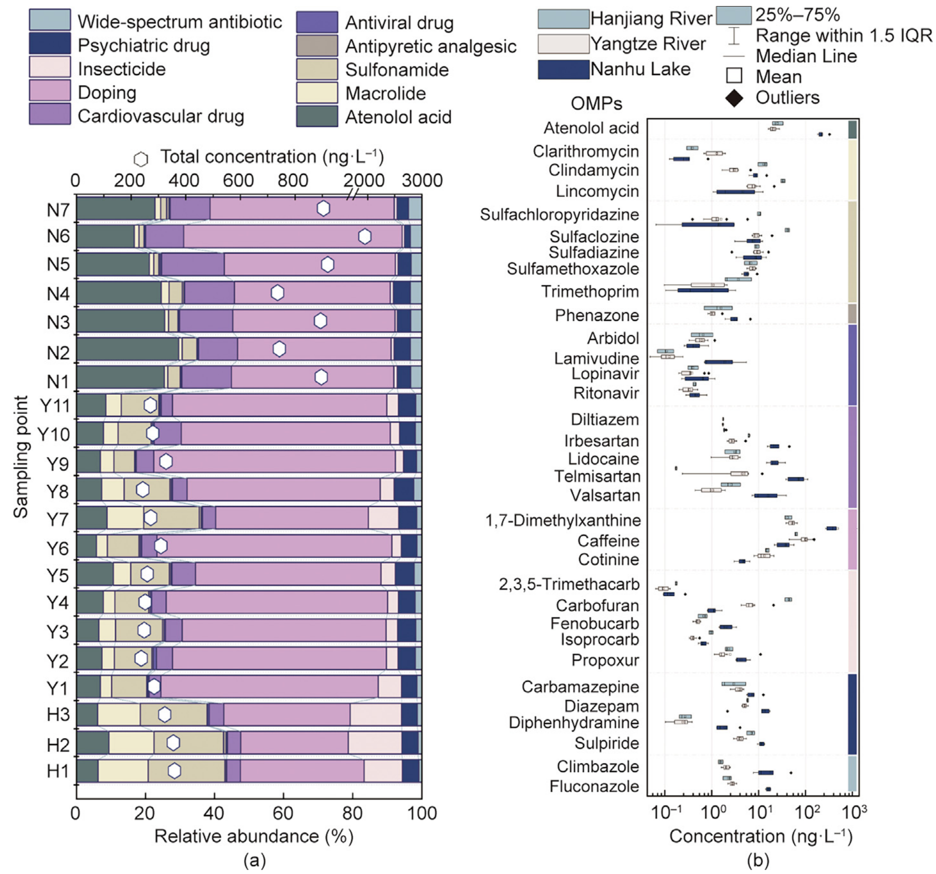

Fig. 1. (a) Compositional profiles and (b) concentrations of 33 OMPs in the Hanjiang River, Yangtze River, and Nanhu Lake in Wuhan in May 2021. IQR: interquartile range.

decreased in May 2021 compared to May 2020, suggesting that the negative effects of the COVID-19 pandemic on the occurrence of OMPs decreased over time. Notably, the concentrations of seven drugs (clarithromycin, lopinavir, irbesartan, primidone, lincomycin, bisacodyl, and valsartan (lower)) in May 2021 were almost the same or lower than in December 2019; however, the concentrations of nine OMPs were higher in May 2021 than those in December 2019 (Fig. 2(a)), indicating that the effects of the pandemic may have lasted for a year. Moreover, compared with December 2019 (Fig. 2(c)), cotinine, telmisartan, and bisacodyl increased by 187 $ng{\cdot}L^{-1}$ (155 fold), 14 $ng{\cdot}L^{-1}$ (66 fold) and 1.86 $ng{\cdot}L^{-1}$ (64 fold), respectively, in May 2020, while lincomycin, caffeine, and 1,7-dimethylxanthine increased by 180 $ng{\cdot}L^{-1}$ (30 fold), 150 $ng{\cdot}L^{-1}$ (five fold) and 31 $ng{\cdot}L^{-1}$ (five fold), respectively. Furthermore, the concentrations of telmisartan and lincomycin were higher downstream than upstream (Figs. 2(d) and (f)), suggesting that their increased contamination in the Yangtze River was caused by discharges from Wuhan.

The concentrations of 11 OMPs, that is, two antivirals (lopinavir and ritonavir), three antihypertensives (valsartan, telmisartan, and losartan), two antibiotics (sulfachloropyridazine and fluconazole), two doping agents (caffeine and cotinine), psychiatric drug (sulpiride), and antipyretic analgesic (naproxen), in Nanhu Lake were significantly higher in May 2020 than in May 2021 (Fig. 3(a)). Moreover, telmisartan and caffeine increa

sed by 346 $ng{\cdot}L^{-1}$ (5.9 fold) and 112 $ng{\cdot}L^{-1}$ (6.1 fold), respectively, while lopinavir and ritonavir increased by 4.3 $ng{\cdot}L^{-1}$ (21 fold) and 0.9 $ng{\cdot}L^{-1}$ (nine fold), respectively (Fig. 3(b)). Furthermore, the OMPs were less affected in Nanhu Lake (11 OMPs) than in the Yangtze River (23 OMPs), but it was obvious that the COVID-19 pandemic could exacerbate the OMP pollution in Nanhu Lake.

The concentrations of 15 OMPs, namely, 3 antivirals (ribavirin, lopinavir, and ritonavir), 4 antihypertensives (telmisartan, irbesartan, valsartan, and losartan), 5 antibiotics (azithromycin, sulfapyridine, lincomycin, sulfamethoxazole, and fluconazole), two doping agents (codeine and cotinine), and psychotropic drug (sulpiride), in WWTP influents were higher in May 2020 (20 380–33 378 $ng{\cdot}L^{-1}$) than in May 2021 (6 759–15 403 $ng{\cdot}L^{-1}$) (Fig. S2 in Appendix A), while the removal efficiencies decreased slightly (90%–94% and 92%–96%, respectively) (Fig. S3 in Appendix A). The high removal efficiencies of OMPs indicate the effective barrier function of WWTPs for OMPs, while the reduced removal efficiency during the COVID-19 pandemic period may be related to the increase in some nondegradable OMPs in the WWTP influent. Furthermore, the removal of individual OMPs by WWTPs ranged from −100% (< −100% was recorded as −100%) to 100% (Fig. S4 in Appendix A), and negative removal values could be explained by the degradation of precursors to target OMPs or the desorption of OMPs from the solid phase to the aqueous phase [39]. In particular, the negative removal efficiencies of lopinavir and ritonavir in May 2020 may be related to the potential refractory behavior of these drugs in WWTPs.

A Venn diagram was constructed to represent the relationship of OMPs (Fig. 3(c)), showing increased concentrations with the Yangtze River, Nanhu Lake and WWTP influent and effluent in May 2020. Seven OMPs were identical compounds that showed elevated concentrations in these four water sample types, suggesting a strong association between them in terms of drug contamination in aquatic environments. Codeine and sulfapyridine were found only in WWTP influents, suggesting that WWTPs are effective in preventing their entry into surface waters. In addition, one and two unique OMPs were found in the WWTP effluent and

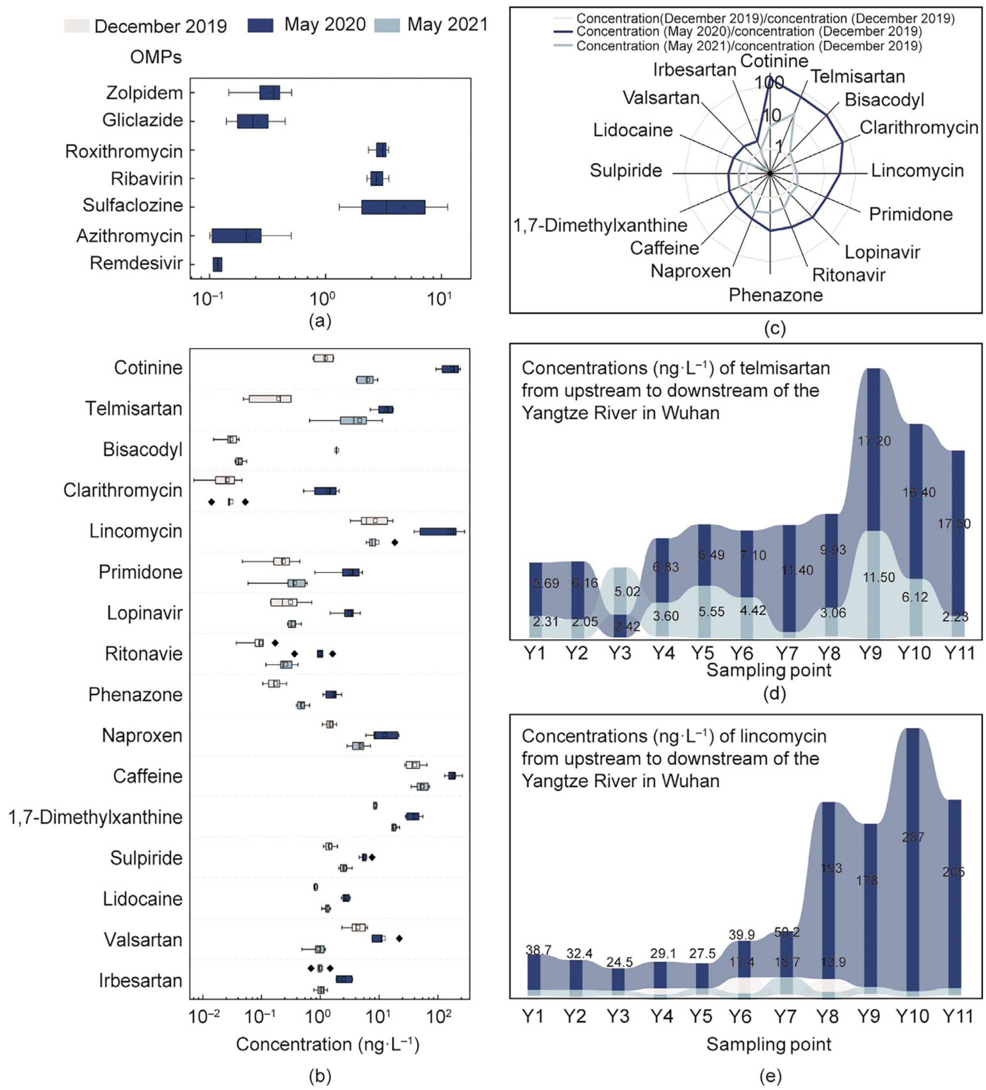

Fig. 2. (a) 7 OMPs detected in the Yangtze River in May 2020. (b) 16 OMPs showed significantly higher concentrations in the Yangtze River in May 2020 than in December 2019 and May 2021. (c) Ratio of the OMP concentration in December 2019, May 2020, and May 2021 to the OMP concentration in December 2019. Concentrations of (d) telmisartan and (e) lincomycin from upstream to downstream of the Yangtze River in December 2019, May 2020, and May 2021.

Nanhu Lake, respectively, while 11 unique OMPs were observed in the Yangtze River, which may be due to the long-term and multiple sources of pollution in this river.

3.3. Pathways of COVID-19 impact on surface water OMP pollution

According to the drug classification, the concentrations of the following drugs increased: four antivirals, ten antibiotics, four antihypertensives, four doping agents and 8 other drugs (Table 1). Telmisartan concentrations in the Yangtze River at the beginning of the COVID-19 pandemic ((0.19 ± 0.13) $ng{\cdot}L^{-1}$) were lower than concentrations found in other surface waters around the world (7–720 $ng{\cdot}L^{-1}$) [40–42], and after the COVID-19 pandemic, the concentration was (13.26 ± 4.40) $ng{\cdot}L^{-1}$, which was in the lower range of concentrations found in other surface waters around the world. At the beginning of the COVID-19 pandemic, ritonavir concentrations in the Yangtze River were (0.10 ± 0.04) $ng{\cdot}L^{-1}$, similar to surface waters in Germany and South Africa [43,44]. In contrast, its concentration after the COVID-19 pandemic was (1.01 ± 0.40) $ng{\cdot}L^{-1}$, lower than those reported in surface waters from Kenya, Zambia, and South Africa [45]. Although the COVID-19 pandemic contributed to the contamination of some OMPs in the Yangtze River, their concentrations were relatively low among the levels reported in surface waters worldwide.

The antivirals lopinavir and ritonavir were prescribed at doses of 800 and 200 mg per person per day, respectively, for COVID-19 treatment [9], and 93% and 38% of the drugs, respectively, were excreted directly in feces and urine without being metabolized in the body [46,47], providing plausible explanations for the increase in their concentration. In addition, ribavirin and remdesivir were used as antiviral agents in COVID-19 treatment in Wuhan [5]. In particular, the concentration of ribavirin in surface water in Wuhan after the COVID-19 pandemic was confirmed to be higher than the detected concentration in previous studies [6]. More than 70% of COVID-19 patients in Wuhan were treated with antibiotics between December 2019 and April 2020 [12], providing a reasonable explanation for the increased antibiotic concentrations in surface waters.

Additionally, the high concentrations of four antihypertensives may be related to their use in COVID-19 treatment, as patients with a history of cardiovascular disease are at high risk of COVID-19 complications [48]. Valsartan has therapeutic benefits in COVID-19 patients, such as cardioprotective, anti-inflammatory, and antifibrotic effects, especially in severe cases

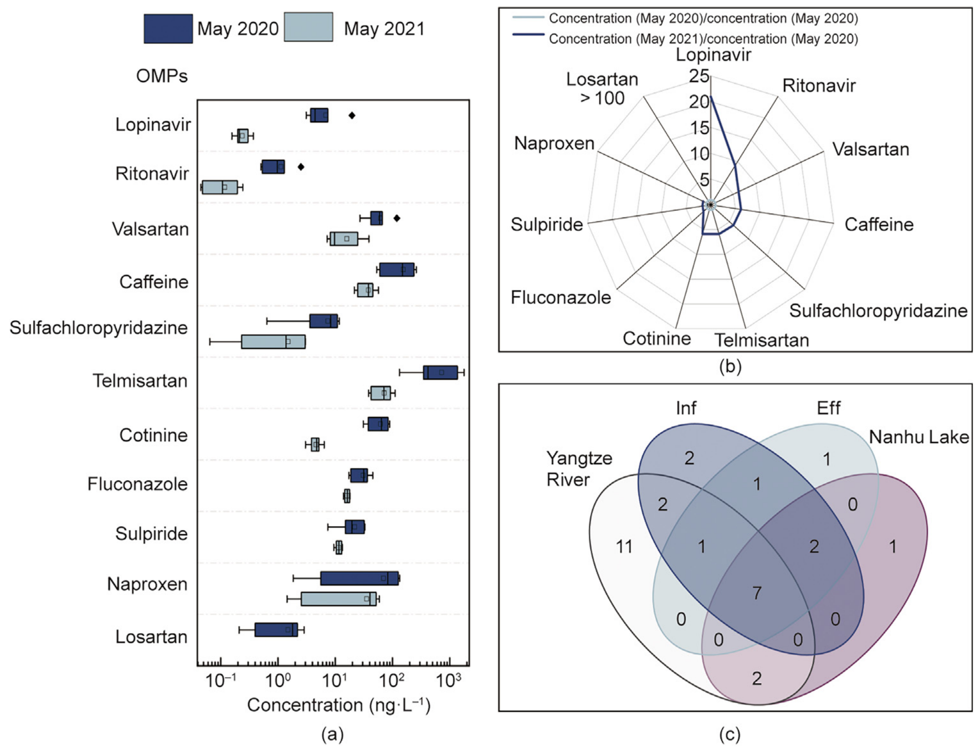

Fig. 3. (a) 11 OMPs showed significantly higher concentrations in Nanhu Lake in May 2020 than in May 2021. (b) Ratio of the OMP concentration in May 2020 and May 2021 to the OMP concentration in May 2021 in Nanhu Lake. (c) Venn diagram showing unique OMPs and shared OMPs with increased concentrations in May 2020 in the Yangtze River, Nanhu Lake, and WWTP influent (Inf) and effluent (Eff).

of induced cardiac injury [49]. Telmisartan reduces morbidity and mortality in hospitalized COVID-19 patients via its anti-inflammatory effects [50], while losartan and irbesartan are also used to treat COVID-19 patients [26]. Approximately 23.2% (about 245 million) of adults aged higher or equal to 18 years in China have hypertension [51], while this proportion is higher in middle-aged and elderly people. Hypertension is a leading risk factor for cardiovascular disease and premature death worldwide [52]. Therefore, drug treatment of hypertension (a major comorbidity in COVID-19 patients) may be responsible for the high concentrations of antihypertensive drugs in surface waters.

Caffeine is an adjuvant used in the treatment of COVID-19 due to its ability to relieve respiratory symptoms and its anti-inflammatory, antioxidant, immunomodulatory, and antiviral effects [53]. 1,7-Dimethylxanthine is the main intermediate of caffeine, and contamination with both compounds may occur simultaneously. In addition, paracetamol, together with codeine, is an effective analgesic for moderate to severe toothache [54]. In the present study, high cotinine concentrations were observed, possibly due to increased smoking, as cotinine is the main byproduct after the primary metabolism of nicotine in the human body. Indirectly supporting our hypothesis, a recent study found that smoking may help to reduce the anxiety associated with COVID-19 [22].

The other eight drugs were potentially related to COVID-19 treatments. In particular, intravenous injection of lidocaine prior to tracheal extubation is effective in reducing emergency cough [55]. Notably, people with mental illness are more susceptible to COVID-19 infection [56]; therefore, the high levels of the psychiatric drug sulpiride may be related to COVID-19 treatment. Naproxen also improves cough and shortness of breath in COVID-19 patients [57]. Phenazone inhibits the major protease of SARS-CoV-2 by interacting with Cys145 and His41 [58], while primidone may be used to treat epileptic COVID-19 patients [59]. Furthermore, zolpidem is a hypnotic used for the short-term treatment of insomnia [60], indicating that the public or COVID-19 patients may suffer from insomnia during the pandemic. Last, gliclazide and bisacodyl are used to treat diabetes and constipation, respectively, and may be relevant to COVID-19 treatment [61,62].

In total, 30 OMPs were found to be elevated in samples taken from WWTPs and surface waters. 26 of these OMPs were elevated in surface waters. Most of the OMPs (22/26) were drugs for the treatment of physical damage, that is, four antivirals, eight antibiotics, four antihypertensives, and six other drugs. The detection of four antihypertensives highlights the need to monitor drugs for comorbidities during a pandemic. Notably, cotinine, a metabolite of nicotine, increased the most (by 187 $ng{\cdot}L^{-1}$, a 155-fold increase), which may be related to increased smoking. In addition, increases in zolpidem and sulpiride may be related to increased insomnia and depression. Therefore, mental shock-induced drug use or behavior in COVID-19 could be considered a nonnegligible pathway for increasing OMP pollution in surface water.

3.4. Ecological risk assessment of OMPs

The RQs of OMPs with significantly high concentrations in May 2020 in the Yangtze River (16 OMPs) and Nanhu Lake (11 OMPs) were calculated to assess the changes in their ecological risks. In the Yangtze River (Fig. 4), the ecological risk level of three OMPs (telmisartan, lopinavir, and ritonavir) evidently changed. The ecological risk levels of telmisartan in December 2019, May 2020, and May 2021 were marginal, medium, and low, respectively, with the values increasing from marginal to medium in May 2020 compared to those in December 2019, thus indicating that the pandemic had a significant impact on the risk level of telmisartan. The high RQ value of telmisartan, which has a high toxicity potential even at low concentrations, can be attributed to its low PNEC [41,68]. In May 2021, telmisartan risk levels remained low and did not return to the marginal level, suggesting that mild effects

Table 1
Classification of 30 drugs that showed increased concentrations in the WWTP influent or effluent, Nanhu Lake (NL), or Yangtze River (YR).

Compound	Detected areas	Symptoms treated	Related to COVID-19	Reference
Antivirals				
Lopinavir	Inf, Eff, NL, YR	COVID-19 infection	Yes	[5]
Ritonavir	Inf, Eff, NL, YR		Yes	[5]
Ribavirin	NL, YR		Yes	[5]
Remdesivir	YR		Yes	[5]
Antibiotics				
Azithromycin	Inf, YR	Bacterial, fungal infections	Yes	[10]
Lincomycin	Inf, Eff, YR		Yes	[25]
Fluconazole	Inf, Eff, NL		Yes	[11]
Sulfamethoxazole	Inf, Eff		Yes	[63]
Sulfapyridine	Inf		Yes	[64]
Sulfadiazine	Eff		Yes	[65]
Sulfachloropyridazine	NL		—	—
Clarithromycin	YR		Yes	[66]
Roxithromycin	YR		—	—
Sulfaclozine	YR		Yes	[67]
Doping				
Codeine	Inf	Cough	Yes	[54]
Cotinine	Inf, Eff, NL, YR	—	—	—
Caffeine	NL, YR	Asthma	Yes	[53]
1,7-Dimethylxanthine	YR	—	—	—
Antihypertensives				
Losartan	Inf, Eff, NL	Hypertension	Yes	[26]
Telmisartan	Inf, Eff, NL, YR		Yes	[50]
Valsartan	Inf, Eff, NL, YR		Yes	[49]
Irbesartan	Inf, YR		Yes	[26]
Others				
Lidocaine	YR	Cough	Yes	[55]
Sulpiride	Inf, Eff, NL, YR	Mental illnesses	Yes	[56]
Naproxen	NL, YR	Cough	Yes	[57]
Phenazone	YR	COVID-19 infection	Yes	[58]
Primidone	YR	Epilepsy	Yes	[59]
Zolpidem	YR	Insomnia	Yes	[60]
Gliclazide	YR	Diabetes	Yes	[61]
Bisacodyl	YR	Constipation	Yes	[62]

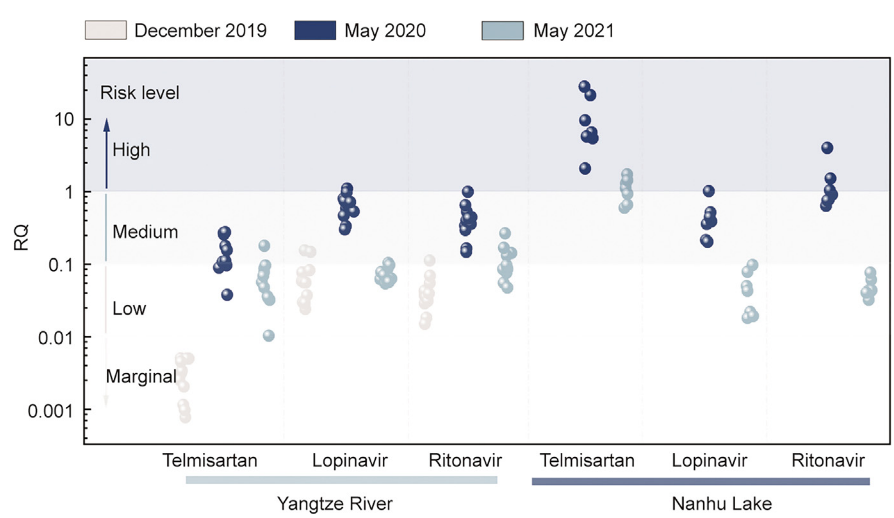

Fig. 4. Changes in the ecological risk of the OMPs in the Yangtze River and Nanhu Lake in Wuhan based on the comparison of RQ values.

of COVID-19 may still be present one year after the end of the first wave of pandemic. Furthermore, the ecological risk levels of ritonavir in December 2019, May 2020, and May 2021 were low, medium, and low/medium, respectively, thus suggesting that high ritonavir concentrations increased its risk level in May 2020 due to the COVID-19 pandemic, and its impact existed even one year after the first wave of pandemic ended. Finally, the ecological risk levels of lopinavir in December 2019, May 2020, and May 2021 were low, medium, and low/medium, respectively. High lopinavir concentrations due to the COVID-19 pandemic may have increased its risk level in May 2020. Later, in May 2021, the risk level of lopinavir returned to the low-risk level, but its RQ value was still slightly higher than that observed in December 2019. This suggests that the negative effects of COVID-19 on lopinavir emergence may persist even a year after the pandemic. These findings are similar to those of a recent study, which reported a medium/high risk of lopinavir and ritonavir two weeks after the COVID-19 pandemic and a low risk eight months after the first wave of pandemic [9]. Elevated environmental risks for telmisartan, lopinavir, and ritonavir in the upper Yangtze River in Wuhan (Y1, Y2, and Y3) (Fig. S1(b)) were evident in May 2020 (compared to December 2019) (Fig. S5 in Appendix A), suggesting that elevated environmental risks for these drugs may be associated with emissions from upstream cities.

Furthermore, the ecological risk levels of telmisartan, lopinavir, and ritonavir in Nanhu Lake were higher in May 2020 than in May 2021. Specifically, telmisartan exhibited high and medium/high ecological risk levels in May 2020 compared to those in May 2021. Thus, Nanhu Lake was in a relatively worse condition than the Yangtze River. Lopinavir exhibited medium/high and low ecological risk levels in May 2020 and May 2021, respectively. Ritonavir showed the same results as lopinavir. These results were highly similar to those of the Yangtze River, thus suggesting that the changes in the risk levels of major OMPs might be widespread in surface waters. Furthermore, the ecological risks in Nanhu Lake were higher than those in the Yangtze River, implying that the OMP pollution in Nanhu Lake was relatively more severe. The RQs for lopinavir and ritonavir decreased almost to a low risk level in May 2021, while the RQs for telmisartan still indicated a medium risk. The study also showed some limitations in the ecological risk assessment. In particular, RQ values were calculated using estimated EC_{50} values rather than measured values, and metabolites of OMPs were not carefully considered.

4. Conclusions

In this study, we monitored 114 OMPs in surface water and WWTPs in Wuhan from 2019 to 2021. Significant increases in 26 OMPs in surface water provided evidence that the COVID-19 pandemic could lead to increased OMP contamination in surface water. Significant increases in four antihypertensives and one antidiabetic drug suggest that pharmacological treatment of comorbidities may contribute to OMPs contamination. Additionally, increases in cotinine, zolpidem, and sulpiride indicate that drugs/behaviors used to protect mental health may also increase OMPs in surface water. When assessing the ecological risks of the observed OMPs, telmisartan, lopinavir, and ritonavir appeared to pose higher ecological risks after the pandemic due to their limited elimination in WWTPs and high ecotoxicity. This study suggests that advanced treatment technologies should be further explored to improve OMP removal in WWTPs during epidemics. Moreover, more comprehensive data on the clinical treatments and environmental risks of pharmaceuticals should probably be collected through multidisciplinary studies in the future to develop environmentally friendly prescription strategies that help to achieve the trade-off between human and environmental health.

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Compliance with ethics guidelines

Jian Zhao, Jin Kang, Xiaofeng Cao, Rui Bian, Gang Liu, Shengchao Hu, Xinghua Wu, Chong Li, Dianchang Wang, Weixiao Qi, Cunrui Huang, Huijuan Liu, and Jiuhui Qu declare that they have no conflict of interest or financial conflicts to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eng.2023.08.020.

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