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Prevalence of Imipenem-Resistant *Acinetobacter baumannii* isolates in Iran: A Meta-Analysis

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ABSTRACT

Background: *Acinetobacter baumannii* is a gram-negative pathogen that is highly resistant to antibiotics. This bacterium can cause severe systemic infections, especially in hospitalized patients. Recently, antimicrobial-resistant *Acinetobacter baumannii* has become a life-threatening pathogen in Iran and around the world.

Materials & Methods: In this study, several Iranian and English databases were systematically searched to find all original and review articles investigating the prevalence of imipenem resistance in their sample size, while mentioning the source of clinical isolates, as well as the prevalence of antimicrobial resistance genes.

Findings: Among genes, bla_{OXA-23} with a prevalence of 31% to 100% was responsible for global outbreaks of imipenem-resistant *Acinetobacter baumannii* and was presented in most of the hospital isolates. Our meta-analysis also revealed that 74.2% of *Acinetobacter baumannii* were resistant to imipenem in 122 clinical studies.

Conclusion: Our study highlighted a rapid increase in the rate of imipenem resistance in clinical isolates of *Acinetobacter baumanni*i in Iran. The need for periodic antibiotic care system programs to monitor the administration and use of antibiotics

Keywords: Imipenem, Resistance, *Acinetobacter baumannii*, Iran.

CITATION LINKS

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Introduction

Acinetobacter baumannii is an opportunistic, nosocomial Gram-negative pathogen that causes severe infections especially in intensive care units (ICUs) [1]. Recently prevalence of multidrug-resistant (MDR) or extensively-drug resistant (XDR) *A. baumannii* becomes a life-threatening problem [2]. Since 1985 the broad-spectrum β-lactam antibiotics e.g. carbapenems such as imipenem, meropenem, ertapenem, and doripenem have been the effective agent against multidrug-resistant *A. baumannii* infections [2, 3]. According to worldwide reports on the prevalence of carbapenem-resistant *A. baumannii*, it can have a negative impact on the treatment of patients [4]. Producing different β-lactamases that harbor insertion sequences (ISs) encoded through mobile elements on integrons, transposons or plasmids genes plays a critical role in carbapenem-resistant *A. baumannii*. Moreover, *A. baumannii* uses different mechanism such as modified penicillin-binding proteins (PBPs) and efflux pumps which decreased cell membranes permeability as well as biofilm formation or mutation in some drug targets to resist and survive in harsh environments (Figure 1) [5]. So, the rapid prevalence of *A. baumannii* strains producing carbapenemases, cephalosporinases (AmpCs), extended-spectrum β-Lactamases (ESBLs), and metallo-β-lactamases (MBLs) is becoming a global concern [6]. During recent years different studies published on the carbapenem-resistant *A. baumannii* in Iran. However, more studies on the mechanism of resistance and prevalence of the resistance bacteria should be done to reach the best treatment strategies for controlling outbreaks of carbapenem-resistant *A. baumannii* [7]. Detection of carbapenem resistance needs phenotypic methods such as disc diffusion and different inhibition tests recommended by CLSI as well as genotypic methods such as PCR to identify carbapenem resistance genes in clinical isolates [8].

This study described the frequency of imipenem-resistant *A. baumannii* in different cities of Iran. So, our aim was to evaluate the distribution and prevalence of resistance genes during the last two decades in Iran.

Materials and Methods

Search Strategies: Our research was performed on several related keywords such as "*A. baumanni*", "carbapenemase", "carbapenem - resistant *A. baumannii*", "prevalence of carbapenem-resistant *A. baumannii* strains in Iran", imipenem", "imipenem resistance", "imipenem resistance in Iran", "multidrug resistance *A. baumanni*i in Iran", which were as inclusion criteria. Keywords were monitored both original and review articles in Persian and English in all research centers e.g. PubMed, MEDLINE, Google Scholar, Iranian data base, Web of sciences, and Scopus during 2006-2020. Out of 483 articles obtained, 143 articles were finally reviewed. For all studies, published date, sample size, and genes related to imipenem were also considered (Table 1).

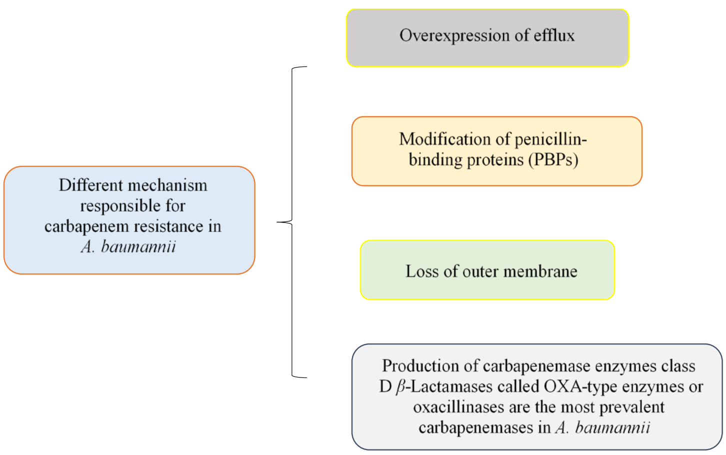

Fig. 1) The most prevalent mechanism of carbapenem resistance in *A. baumannii* [9]

Table1) Studies included on resistance of *A. baumannii* to imipenem in Iran.

Author	Year	City	Sample size	No. of Imipenem resistant isolates	%	Isolated from	Ref
Sadeghifard et al.,	2006	Tehran	66	66	100	NR	[10]
Ardebili et al.,	2012		65	60	92.38	Burned or hospitalized patients in ICU	[11]
Davoodi et al.,	2015		104	70	67.30	Clinical isolates	[12]
Dehghani et al.,	2012		50	39	78	Blood, respiratory secretions, urine, skin ulcer, and oral mucosa	[13]
Erfani et al.,	2017		107	NR*	NR	Clinical isolates	[14]
Dehbalaei et al.,	2017		48	37	77.08	Wound, trachea, urine, catheter, sputum, and burn	[15]
Mirnejad et al.,	2012		50	39	78	Blood, tracheal, wound swab samples, urine and five samples with unknown origin	[16]
Karmostaji et al.,	2013		123	103	83.74	Aspirated sputum, trachea, burn, wound and urinary tract infections	[17]
Pajand et al.,	2013		75	64	85.33	Aspirates, urine, wound, blood and sputum, burn wound	[18]
Azimi et al.,	2015		65	65	100	Burn wound	[19]
Alavi-Moghadam et al.,	2014		61	61	100	Ventilator associated pneumonia. Sputum, wounds, urine, central venous line, blood	[20]
Saderi et al.,	2015		106	102	96.22	Clinical isolates	[21]
Sharif et al.,	2014		200	171	85.5	Endotracheal biopsy, sputum, blood, catheter, urine, wound	[22]
Fallah et al.,	2014		108	99	91.66	Urinary specimens	[23]
Bahador et al.,	2015		62	38	61.29	ICU patients	[24]
Haeili et al.,	2013		136	102	75	Broncho alveolar lavage (BAL), mini BAL, tracheal aspirates, and sputum	[25]
Goudarzi et al.,	2013		221	214	96.83	Specimens, environmental isolates which were obtained from patients' surroundings, medical equipment and hands of staff	[26]

Continue Table1) Studies included on resistance of *A. baumannii* to imipenem in Iran.

Author	Year	City	Sample size	No. of Imipenem resistant isolates	%	Isolated from	Ref
Goudarzi et al.,	2016		108	NR	NR	Blood, wound, urine, sputum and respiratory tract	[27]
Maspi et al.,	2016		86	78	90.69	NR	[28]
Malayeri et al.,	2016		60	51	85	Clinical samples	[29]
Khaledi et al.,	2016		100	NR	NR	ICU patients	[30]
Zanganeh et al.	2015		58	58	100	Burn and non-burn isolates of hospitalize patients	[31]
Azimi et al.,	2013		93	80	86.02	Burn wounds	[32]
Khalilzadegan et al.,	2016		131	131	100	ICU patients	[33]
Azimi et al.,	2012		7	6	85.72	Burn wounds, environmental isolates which were obtained from patients' surroundings, medical equipment	[34]
Azimi et al.,	2016		50	NR	NR	Burn patients	[35]
Owlia et al.,	2012		126	107	84.92	Burn wounds	[36]
Asadollahi et al.,	2012		23	11	47.82	Burn wounds	[37]
Aminzadeh et al.,	2012		39	16	41.02	CSF	[38]
Vafaei et al.,	2013		100	76	76	Burn wounds	[39]
Talebi-Taher et al.,	2012		34	34	100	Endobronchial aspirates	[40]
Mirnejad et al.,	2013		50	39	78	Sputum, trachea, wounds, urine, blood	[41]
Asadollahi et al.,	2011		100	49	49	Clinical isolates	[42]
Shahcheraghii et al.,	2011		203	100	43.47	Blood, wound, urine, sputum, and respiratory tract	[43]
Mohammadi et al.,	2017		103	96	93.20	Ventilated patients	[44]
Mohammadi et al.,	2016		100	98	98	Burn wounds	[45]
Babapour et al.,	2017		156	142	91.02	Blood, burn wound, urine, sputum, and respiratory tract, CSF	[46]

Continue Table1) Studies included on resistance of *A. baumannii* to imipenem in Iran.

Author	Year	City	Sample size	No. of Imipenem resistant isolates	%	Isolated from	Ref
Tarashi et al.,	2016		189	187	98.94	Burn wounds	[47]
Jazani et al.,	2011		48	7	14.58	Burn wounds	[48]
Asadollahi et al.,	2011		100	39	39	Clinical isolates	[49]
Vahdani et al.,	2011		101	19	18.81	Respiratory tube, urine, wound, and blood	[50]
Mohammadtaheri et al.,	2010		136	126	92.64	Respiratory tube, urine, blood wound	[51]
Akbari et al.,	2010		100	53	53	Wound, trachea, pleural fluid, blood, sputum, urine, catheter, CSF	[52]
Moradi–Tabriz et al.,	2010		166	45	27.10	Blood	[53]
Rahbar et al.,	2010		88	1	1.13	Respiratory tube, urine, blood, wound	[54]
Rahbar et al.,	2011		88	4	4.54	Respiratory tract, urine, blood, wound and other clinical specimens	[55]
Goudarzi et al.,	2015		128	127	99.21	ICU patients	[56]
Soroush et al.,	2009		145	73	50.34	NR	[57]
Aliamezani et al.,	2016		8	5	62.50	Environmental surfaces and equipment	[58]
Taherikalani et al.,	2009		80	42	52.50	Clinical isolates	[59]
Owrang et al.,	2017		105	103	98.09	Clinical isolates	[60]
Peerayeh et al.,	2015		123	123	100	Sputum, urine, CSF and pleural effusion	[61]
Noori et al.,	2014		84	67	79.76	NR	[62]
Zafari et al.,	2017		536	429	80.03	Hospitalized patients	[63]
Navidinia et al.,	2017		37	32	86.48	Trachea, urine, wound, discharges, ascites fluid, pleural fluid, blood, synovial fluid, and catheter	[64]
Shahcheraghi et al.,	2009		95	65	68.42	ICU patients	[65]
Mirshekar et al.,	2017		72	61	84.72	NR	[66]

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Continue Table1) Studies included on resistance of *A. baumannii* to imipenem in Iran.

Author	Year	City	Sample size	No. of Imipenem resistant isolates	%	Isolated from	Ref
Tavakol et al.,	2014		121	NR	NR	Clinical isolates	[67]
Momtaz et al.,	2017		121	NR	NR	Blood, phlegms, urine, CSF, pus	[68]
Boroumand et al.,	2009		191	47	24.60	Clinical isolates	[69]
Aghamiri et al.,	2015		176	169	96.02	Hospitalized patients	[70]
Beigverdi et al.,	2019		6281	4899	77.99	NR	[71]
Hosseini-Jazani et al.,	2009		48	7	14.58	Burn ward	[72]
Pournajafi et al.	2019		73	22		Burn wounds	[73]
Feizabadi et al.,	2008		108	55	50.92	Wounds, trachea, blood, CSF, urine, other tissues	[74]
Farshadzadeh et al.,	2015		92	NR		Burn wounds	[75]
Gholami et al.,	2020		60	60	100	Burn wounds	[76]
Rahbaar et al.,	2007		65	18	27.69	Hospitalized patients	[77]
Mahdian et al.,	2015		37	NR	NR	Burn wounds	[78]
Tafreshi et al.,	2019		84	31	36.90	Wound infections	[79]
Savari et al.,	2017		120	NR	NR	Tracheal aspiration, blood, CSF, burn wound, urine infections	[80]
Nasrolahei et al.,	2014	Tehran/ Sari	100	67	67	ICU patients	[81]
Hojabri et al.,	2014	Tehran/ Tabriz	71	60	84.50	Clinical isolates	[82]
Rahmani et al.,	2015	Tehran/ Shiraz	140	129	92.14	Hospitalized patients	[83]
Peymani et al.,	2012	Tabriz	134	74	55.22	Hospitalized patients	[84]

Continue Table1) Studies included on resistance of *A. baumannii* to imipenem in Iran.

Author	Year	City	Sample size	No. of Imipenem resistant isolates	%	Isolated from	Ref
Peymani et al.,	2011		100	54	54	Tracheal aspirate, urine, blood, bronchial washing, wound, sputum, abscess drainage, CSF, catheter, pleural effusion, and ascites	[85]
Sohrabi et al.,	2012		100	62	62	Blood, tracheal aspirates, wound, sputum, abscess drainage, wound, bronchial washing, urine	[86]
Ranjbar et al.,	2019	Markazi, Khozestan, Kermanshah	163	154	94.47	Wound infections	[87]
Ezadia et al.,	2019	Gorgan	71	44	61.97	Urine, respiratory tract secretions, blood, and wound swab	[88]
Shirmohammadlou et al.,	2018	Zanjan	100	100	100	Blood, sputum, wound swabs, chest tube secretions and urine	[89]
Khosroshahi et al.,	2020	Qazvin	15	4	26.66	ICU patients	[90]
Farsiani et al.,	2015	Mashhad	36	32	88.88	Different wards of a teaching hospital	[91]
Salimizand et al.,	2016		30	NR	NR	patients and environmental specimens	[92]
Sarhaddi et al.,	2017		54	54	100	Burn wounds	[93]
Alaei et al.,	2013	Shiraz	85	43	50.58	ICU patients	[94]
Alaei et al.,	2016		85	79	92.94	Isolates from patients in a tertiary care hospital	[95]
Japoni et al.,	2011		79	18	22.78	Blood, urine wound and sputum	[96]
Pourabbas et al.,	2016		61	NR	NR	patients with blood infections	[97]
Moghadam et al.,	2016		96	95	98.95	Clinical specimens	[98]
Jafari et al.,	2013		63	26	41.27	Clinical specimens	[99]
Kooti et al.,	2015		200	199	99.50	Urine, wound, blood, sputum, ETT, body fluid, nose, throat and eye	[100]
Sarikhani et al.,	2017	Qom	108	97	89.81	Tracheal aspirate, urine, blood, wounds and CSF	[101]
Shoja et al.,	2013	Ahvaz	206	198	96.11	Clinical specimen	[102]

Continue Table1) Studies included on resistance of *A. baumannii* to imipenem in Iran.

Author	Year	City	Sample size	No. of Imipenem resistant isolates	%	Isolated from	Ref
Shoja et al.,	2016		124	97	78.22	Clinical specimen	[103]
Shoja et al.,	2017		40	36	90.00	Wound, skin biopsy, blood	[9]
Moosavian et al.,	2017		151	142	94.04	Clinical specimens	[104]
Amin et al.,	2019		85	69		Burn wounds, tracheal secretion, blood, bronchial lavage, urine	[105]
Salimizand et al.,	2014	Kerman	40	13	32.50	Tracheal, urine, wound, Blood, CSF	[106]
Saffari et al.,	2017		64	NR	NR	Clinical Isolates	[107]
Azizi et al.,	2015		65	NR	NR	Blood, lung of the patient with ventilator and URI	[108]
Mohajeri et al.,	2014	Kermanshah	104	83	79.80	Sputum, blood, urine clinical specimens	[109]
Mohajeri et al.,	2017		75	62	82.66	Blood, sputum, wounds, urine, abdominal abscesses, synovia	[110]
Mohajeri et al.,	2015		42	38	90.47	Clinical specimens	[111]
Norozi et al.,	2014		84	67	79.76	Sputum, blood and urine	[112]
Salimizande et al.,	2014	Kurdistan	54	28	51.85	Environmental specimens	[106]
Karbasizade et al.	2012	Isfahan	50	26	52	ICU patients	[113]
Rezaei et al.,	2018		153	153	100	Various clinical sources	[114]
Ghalebi et al.,	2017		40	40	100	ICU patients	[115]
Ghajavand et al.,	2014		43	40	93.02	ICU specimens	[116]
Vazirzadeh et al.,	2015		100	96	96.00	Clinical samples	[117]
Shamsizadeh et al.,	2017		40	34	85.00	ICU, surgery wards (SW), and internal medicine wards (IM)	[118]
Shokri et al.,	2017		31	28	90.33	Different clinical specimens	[119]
Safari et al.,	2013	Hamedan	100	85	85.00	Trachea, blood, urine, sputum and wound samples of patients bedridden in ICU	[120]

Continue Table1) Studies included on resistance of *A. baumannii* to imipenem in Iran.

Author	Year	City	Sample size	No. of Imipenem resistant isolates	%	Isolated from	Ref
Bardbari et al.,	2017		75	73	97.33	Sputum, bronchoalveolar lavage, and endotracheal aspirates of the patients hospitalized at ICU wards	[121]
Safari et al.,	2015		100	95	95.00	ICU wards	[122]
Khalatabadi-Farahani et al.,	2009	Kashan	48	10	20.83	Blood, urine, CSFs, sputum, pleural fluid	[123]
Josheghani et al.,	2017		40	40	100	Tracheal tubes of patients hospitalized in the ICU	[124]
Goli et al.,	2017		124	111	89.51	Blood, urine, trachea, Ascites, sputum, catheters	[125]
Bagheri et al.,	2015		124	110	88.71	Hospitalized patients	[126]
Japoni et al.,	2013	Arak	56	47	83.92	Hospitalized patients	[127]
Japoni et al.,	2014		56	NR	NR	Hospitalized patients	[128]
Bahadori et al.,	2015	Bandar-Abbas	72	70	97.22	Hospitalized patients	[129]
Moosavian et al.,	2020		124	92	74.2	Hospitalized patients	[130]

NR: Not Reported, ICU: Intensive care unit, CSF: cerebra spinal fluid, URI: Upper Respiratory Infection, ETT: endotracheal tube

Data Extraction, Synthesis and Analysis: We reported our data in the following way: first author, city, sample size, the status and prevalence of resistance to imipenem. Statistical analysis was performed by Comprehensive Meta-Analysis Software Version 2.0 (Biostat, Englewood, NJ). The prevalence was reported with 95% confidence intervals (CIs). Random effects models were used. To assess the potential risk of publication bias, Begg rank correlation regression methods were used (P<0.05) and were considered indicative of a statistically significant publication bias.

Findings

The result of the search strategies yielded 122 articles that reported the prevalence of imipenem-resistant *A. baumannii* in Iran (Table 1). Most of the studies were performed in central Iran (e.g. Tehran, n=71). Figure 2 shows the forest plot from the meta-analysis of antimicrobial resistance of *A. baumannii* to imipenem, resulting in prevalence of 74.2% (95% CI, 69.7–78.2). As shown in Figure 3, based on the funnel plot of meta-analysis, some evidence for the publication bias was observed. The estimated ranks of correlation coefficients of Begg were 0.742. Figure 4 also shows genes responsible for imipenem-resistant *A. baumannii* associated with their prevalence. Figure 5 also displays the prevalence of imipenem-resistant clinical isolates of in different cities of Iran.

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Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value	Relative weight	Relative weight
Sadeghifard et al., 2006	0.993	0.892	1.000	3.445	0.001	0.02	
Ardebili et al., 2012	0.923	0.828	0.968	5.338	0.000	0.20	
Davoodi et al., 2015	0.673	0.577	0.756	3.455	0.001	0.99	
Dehghani et al., 2012	0.780	0.645	0.874	3.707	0.000	0.37	
Erfani et al., 2017	0.005	0.000	0.070	-3.789	0.000	0.02	
Dehbalaei et al., 2017	0.771	0.632	0.868	3.532	0.000	0.37	
Mirnejad et al., 2012	0.780	0.645	0.874	3.707	0.000	0.37	
Karmostaji et al., 2013	0.837	0.761	0.893	6.707	0.000	0.72	
Pajand et al., 2013	0.853	0.754	0.917	5.395	0.000	0.41	
Azimi et al., 2015	0.992	0.890	1.000	3.434	0.001	0.02	
Alavi-Moghadam et al., 2014	0.992	0.884	0.999	3.389	0.001	0.02	
Saderi et al., 2015	0.962	0.904	0.986	6.354	0.000	0.17	
Sharif et al.,2014	0.855	0.799	0.897	8.835	0.000	1.07	
Fallah et al.,2014	0.917	0.848	0.956	6.887	0.000	0.36	
Bahador et al.,2015	0.613	0.487	0.725	1.762	0.078	0.63	
Haeili et al.,2013	0.750	0.671	0.816	5.548	0.000	1.10	
Goudarzi et al.,2013	0.968	0.935	0.985	8.904	0.000	0.29	
Goudarzi et al.,2016	0.005	0.000	0.069	-3.795	0.000	0.02	
Maspi et al.,2016	0.907	0.825	0.953	6.134	0.000	0.31	
Malayeri et al.2016	0.850	0.736	0.920	4.798	0.000	0.33	
Khaledi et al., 2016	0.005	0.000	0.074	-3.741	0.000	0.02	
Zanganeh et al.,2015	0.992	0.879	0.999	3.353	0.001	0.02	
Azimi et al., 2013	0.860	0.774	0.917	6.076	0.000	0.48	
Sadeh et al., 2013	0.996	0.942	1.000	3.933	0.000	0.02	
Azimi et al.,2012	0.857	0.419	0.980	1.659	0.097	0.04	
Azimi et al., 2016	0.010	0.001	0.138	-3.247	0.001	0.02	
Owlia et al., 2012	0.849	0.776	0.902	6.943	0.000	0.70	
Asadollahi et al., 2012	0.478	0.288	0.675	-0.208	0.835	0.25	
Aminzadeh et al., 2012	0.410	0.269	0.568	-1.115	0.265	0.41	
Vafaei et al., 2013	0.760	0.667	0.834	4.923	0.000	0.79	
Talebi-Taher et al., 2012	0.986	0.809	0.999	2.973	0.003	0.02	
Mirnejad et al., 2013	0.780	0.645	0.874	3.707	0.000	0.37	
Asadollahi et al., 2011	0.490	0.394	0.587	-0.200	0.841	1.08	
Shahcheraghii et al., 2011	0.493	0.424	0.561	-0.211	0.833	2.19	
Mohammadii et al., 2017	0.932	0.864	0.967	6.688	0.000	0.28	
Mohammadi et al., 2017	0.980	0.924	0.995	5.449	0.000	0.08	
Babapour et al., 2017	0.910	0.854	0.946	8.270	0.000	0.55	
Tarashi et al., 2016	0.989	0.959	0.997	6.384	0.000	0.09	
Jazani et al., 2011	0.146	0.071	0.276	-4.322	0.000	0.26	
Asadollahii et al., 2011	0.390	0.300	0.489	-2.182	0.029	1.03	
Vahdani et al.,2011	0.188	0.123	0.276	-5.743	0.000	0.67	
Mohammadtaheri et al., 2010	0.926	0.869	0.960	7.712	0.000	0.40	
Akbari et al., 2010	0.530	0.432	0.625	0.600	0.549	1.08	
Moradi–Tabriz et al., 2010	0.271	0.209	0.344	-5.665	0.000	1.42	
Rahbar et al., 2010	0.011	0.002	0.076	-4.440	0.000	0.04	
Jazani et al.,2011	0.146	0.071	0.276	-4.322	0.000	0.26	
Rahbar et al., 2011	0.045	0.017	0.115	-5.949	0.000	0.16	
Goudarzi et al.,2015	0.992	0.947	0.999	4.825	0.000	0.04	
Soroush et al.,2010	0.503	0.423	0.584	0.083	0.934	1.56	
Aliamezani et al., 2016	0.625	0.285	0.875	0.699	0.484	0.08	
Taherikalani et al., 2009	0.525	0.416	0.632	0.447	0.655	0.86	
Owrang et al., 2017	0.981	0.927	0.995	5.521	0.000	0.08	
Peerayeh et al.,2015	0.996	0.939	1.000	3.888	0.000	0.02	
Noori et al., 2014	0.798	0.698	0.870	5.050	0.000	0.59	
Zafari et al., 2017	0.800	0.764	0.832	12.851	0.000	3.70	
Navidinia et al., 2017	0.865	0.714	0.943	3.860	0.000	0.19	
Shahcheraghi et al., 2009	0.684	0.584	0.770	3.503	0.000	0.89	
Mirshekar et al., 2017	0.847	0.745	0.913	5.229	0.000	0.40	
Boroumand et al., 2009	0.246	0.190	0.312	-6.665	0.000	1.53	
Aghamiri et al., 2015	0.960	0.919	0.981	8.255	0.000	0.29	
Beigverdi et al.,2019	0.780	0.770	0.790	41.548	0.000	46.52	
Hosseini-Jazani et al., 2009	0.146	0.071	0.276	-4.322	0.000	0.26	
Pournajafi et al.,2019	0.301	0.207	0.416	-3.296	0.001	0.66	
Feizabadi et al., 2008	0.509	0.416	0.602	0.192	0.847	1.16	
Farshadzadeh et al., 2015	0.005	0.000	0.080	-3.681	0.000	0.02	
Gholami et al., 2015	0.992	0.882	0.999	3.377	0.001	0.02	
Rahbaar et al.,	0.277	0.182	0.397	-3.463	0.001	0.56	
Mahdian et al., 2015	0.013	0.001	0.178	-3.033	0.002	0.02	
Tafreshi et al., 2019	0.369	0.273	0.477	-2.372	0.018	0.84	
Savari et al., 2017	0.004	0.000	0.063	-3.870	0.000	0.02	
Nasrolahei et al., 2014	0.670	0.572	0.755	3.330	0.001	0.95	
Hojabri et al., 2014	0.845	0.741	0.912	5.172	0.000	0.40	
Rahmani et al., 2015	0.921	0.864	0.956	7.838	0.000	0.44	
Peymani et al., 2012	0.552	0.467	0.634	1.207	0.227	1.43	
Peymani et al., 2011	0.540	0.442	0.635	0.799	0.424	1.07	
Sohrabi et al., 2012	0.620	0.521	0.710	2.376	0.017	1.02	
Ranjbar et al. 2019,	0.945	0.897	0.971	8.281	0.000	0.37	
Ezadia et al., 2019	0.620	0.502	0.725	1.998	0.046	0.72	
Shirmohammadlou et al.,2018	0.995	0.926	1.000	3.741	0.000	0.02	
Khosroshahi et al., 2007	0.267	0.104	0.533	-1.733	0.083	0.13	
Farsiani et al., 2015	0.889	0.739	0.958	3.921	0.000	0.15	
Salimizand et al., 2016	0.016	0.001	0.211	-2.883	0.004	0.02	
Sarhaddi et al., 2017	0.991	0.871	0.999	3.302	0.001	0.02	
Alaei et al., 2013	0.506	0.401	0.610	0.108	0.914	0.92	
Alaei et al., 2016	0.929	0.852	0.968	6.087	0.000	0.24	
Japoni et al., 2011	0.228	0.149	0.333	-4.550	0.000	0.60	
Pourabbas et al., 2016	0.008	0.001	0.116	-3.389	0.001	0.02	
Moghadam et al., 2016	0.990	0.930	0.999	4.530	0.000	0.04	
Jafari et al., 2013	0.413	0.299	0.537	-1.379	0.168	0.66	
Kooti et al., 2015	0.995	0.965	0.999	5.280	0.000	0.04	
Sarikhani et al., 2017	0.898	0.825	0.943	6.842	0.000	0.43	
Ahmadi et al., 2014	0.767	0.619	0.870	3.307	0.001	0.33	
Shoja et al., 2013	0.961	0.924	0.980	8.898	0.000	0.33	
Shoja et al., 2016	0.782	0.701	0.846	5.877	0.000	0.91	
Shoja et al., 2017	0.900	0.762	0.962	4.169	0.000	0.16	
Moosavian et al., 2017	0.940	0.889	0.969	8.025	0.000	0.37	
Amin et al.,2019	0.812	0.715	0.881	5.267	0.000	0.56	
Salimizand et al., 2014	0.325	0.199	0.483	-2.165	0.030	0.38	
Saffari et al., 2017	0.008	0.000	0.111	-3.423	0.001	0.02	
Azizi et al., 2015	0.008	0.000	0.110	-3.434	0.001	0.02	
Mohajeri et al., 2014	0.798	0.710	0.864	5.626	0.000	0.72	
Mohajeri et al., 2017	0.827	0.724	0.897	5.121	0.000	0.46	
Mohajeri et al., 2015	0.905	0.772	0.964	4.283	0.000	0.16	
Norozi et al., 2014	0.798	0.698	0.870	5.050	0.000	0.59	
Salimizande et al., 2014	0.519	0.387	0.647	0.272	0.786	0.58	
Karbasizade et al.,2012	0.520	0.383	0.654	0.283	0.777	0.54	
Rezaei et al.,2018	0.997	0.950	1.000	4.043	0.000	0.02	
Ghalebi et al., 2017	0.988	0.833	0.999	3.088	0.002	0.02	
Ghajavand et al., 2014	0.930	0.805	0.977	4.327	0.000	0.12	
Vazirzadeh et al., 2015	0.960	0.898	0.985	6.228	0.000	0.17	
Shamsizadeh et al., 2017	0.850	0.704	0.931	3.917	0.000	0.22	
Shokri et al., 2017	0.903	0.739	0.968	3.677	0.000	0.12	
Safari et al., 2013	0.850	0.766	0.908	6.194	0.000	0.55	
Bardbari et al., 2017	0.973	0.900	0.993	5.019	0.000	0.08	
Safari et al., 2015	0.950	0.885	0.979	6.417	0.000	0.21	
Khalatabadi-Farahani et al., 2009	0.208	0.116	0.346	-3.756	0.000	0.34	
Josheghani et al., 2017	0.988	0.833	0.999	3.088	0.002	0.02	
Goli et al., 2017	0.895	0.828	0.938	7.316	0.000	0.50	
Bagheri et al., 2015	0.887	0.818	0.932	7.265	0.000	0.54	
Japoni et al., 2013	0.839	0.719	0.914	4.543	0.000	0.33	
Japoni et al., 2014	0.009	0.001	0.125	-3.328	0.001	0.02	
Bahadori et al., 2015	0.972	0.896	0.993	4.958	0.000	0.08	
	0.728	0.719	0.736	47.277	0.000		

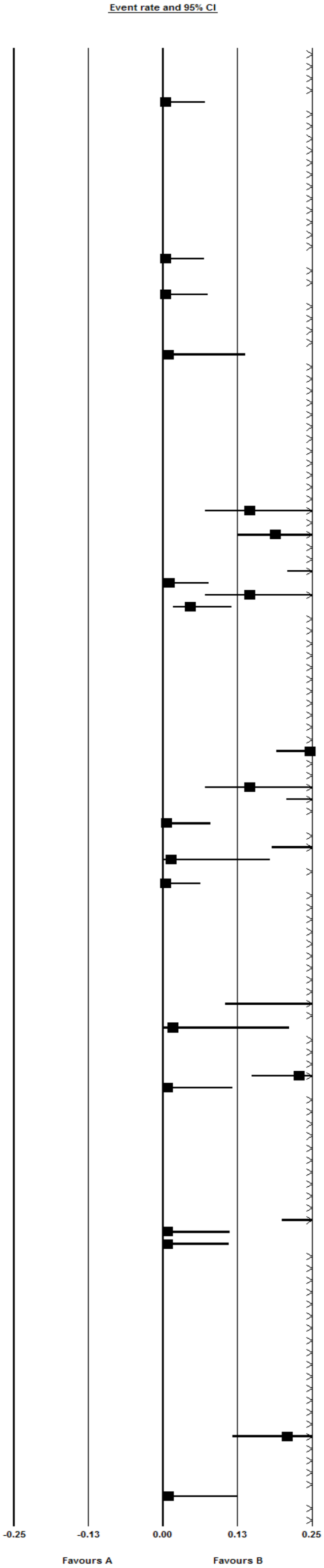

Fig. 2) Forest plot of the meta-analysis of imipenem resistance in *A. baumannii*. CI: confidence interval.

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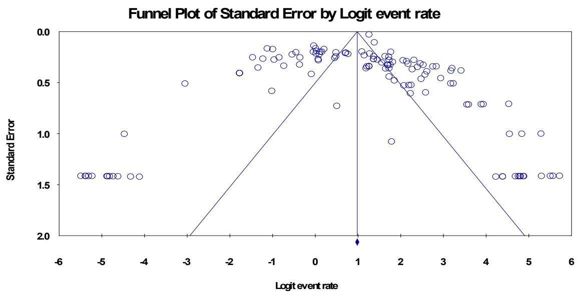

Fig. 3) Funnel plot of the meta-analysis of imipenem resistance in *A. baumannii*.

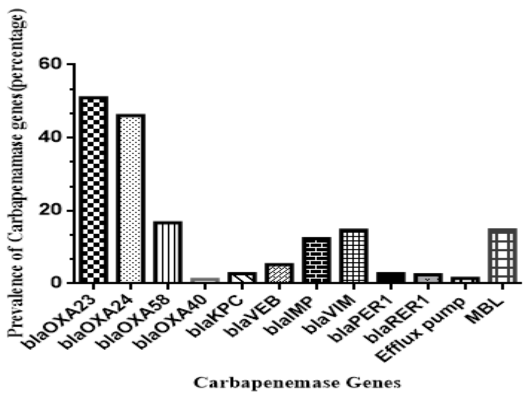

Fig. 4) Genes responsible for carbapenem resistance in *A. baumannii*

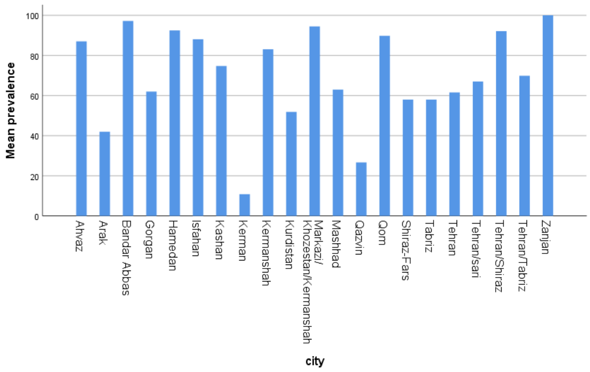

Fig. 5) Prevalence of carbapenem-resistant clinical isolates of *A. baumanii* in different cities of Iran

Discussion

A. baumannii is a multidrug-resistant nosocomial pathogen that causes severe infections among patients especially in ICU and can hydrolyze various β-lactam antibiotics by different enzymes such as carbapenemases [131, 132]. Among bacteria, resistance to carbapenems, especially imipenem, has been reported from various countries as well as in Iran [133-135]. Recently due to resistance of *A. baumannii* to a wide range of antimicrobial agents, raise a concern on controlling life-threatening infections worldwide [136].

Our meta-analysis declared a pooled frequency resistance rate to imipenem (74.2%), which is lower when compared with some studies in Iran [137]. One strategy for preventing the spread of carbapenem resistance from our neighboring countries e.g. Pakistan and Iraq, which has a high prevalence of multidrug resistance *A. baumannii*, is implementation of typing methods [138]. In recent years carbapenem resistance in *A. baumannii* isolates are increasing in the world. Various factors have been mentioned to contribute to this outbreak, for example, inadequate implementation of treatment instructions and protocols, excessive use of antimicrobial agents in health care systems or the community [139, 140]. It is suggested that controlling policy including standard administration guidelines together with the suitable drug, dosage as well as the duration of treatment should meticulously be monitored in order to prevent the emergence of resistance among bacteria.

Our current study has evaluated the prevalence of imipenem- resistant in *A. baumannii* strains in different cities of Iran. The results showed that this resistance has increased in recent decades and there is a need for more prevention and monitoring to overcome infections caused by the bacterium.

Our findings also declared that imipenem-resistant *A. baumannii* isolates harboring *bla*$_{OXA-23}$ are the most among the strains. Similar to other studies, our study indicated a sporadic distribution of MBL genes of *A. baumannii* in Iran. However, *bla*$_{OXA-23}$ has the highest prevalence distribution gene in Iran that is responsible for carbapenem-resistant *A.baumannii* as well as several

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Asian countries [9, 141]. Other reports have indicated the prevalence of MBL gene among carbapenem-resistant isolates, which were significant at the second level. Sometimes phenotypic tests in the evaluation of antibiotic resistance may be reported as false negative or low-level resistance.

To date, several mechanisms have been implicated in carbapenem-resistant isolates, including modification of PBPs, reduction of outer membrane purines, low permeability, and degradation of AmpC β-lactamase. However, the reason for this requires further studies to more accurately assess the mechanisms of resistance among bacteria, especially imipenem-resistant *A. baumannii* [9, 142]. In this study, we focused on bla_{OXA-23}, bla_{OXA-24}, $bla_{OXA-58,}$ and MBL genes and the distribution of them among nosocomial isolates of *A. baumannii.* Treatment of imipenem-resistant *A. baumannii* gets complicated due to location of carbapenemase on mobile elements and high level of abuse clinically prescribing carbapenem antibiotic and this lead to the high activity of OXA genes as well as high carbapenem-resistant isolates [141].

It should be said the main gene involved in this resistance was *OXA*23, which was present in all reviewed articles, while *OXA*24 and *OXA*58 were reported sporadically. Statistics also showed the highest prevalence of imipenem resistance was in Zanjan and Bandar-Abbas provinces was in the second level. Kerman showed the least prevalence among cities. It seems that sufficient study or the size of non-uniform samples can be effective in statistical analysis. As the statistics confirmed the distribution of *OXA* genes especially *OXA*23 among isolates, it seems that the gene plays a critical role in imipenem resistance of *A. baumannii.* MBL genes are also important in resistance characteristics of *A. baumanni*i to imipenem but at a lower level in comparison to *OXA* genes. However, this issue needs more studies. The distribution and transmission of *OXA* and *MBL* genes by plasmids, integrons, or other mobile elements should be also investigated. As a result, resistance to imipenem, VIM, and NDM has been increasing in recent years, and this could be a warning sign for the overuse of antibiotics to treat *A. baumannii* infections.

Conclusion

All in all, it can be said *A.baumanni*i is an important global pathogen with the ability to resistant to different antibiotics and this can be an alarm for health care causing high mortality and morbidity and is a problematic microorganism during recent decades. Our study demonstrated the rapid spread of β-lactamase genes of *OXA* and *MBL* in hospitals of Iran between"2006 to 2020" and declares the significant role of them in resistance to carbapenems especially imipenem. Overall, prescription antibiotics in Iran should be frequently monitored and evaluated, resulting in a limited transfer of antibiotic resistance genes among multidrug-resistant *A. baumanni*i.

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Authors' Contributions: Conceptualization: MDS; Data curation and formal analysis: LH; Investigation: MDS, LH; Methodology and project administration: MDS, LH, SS; Supervision: SS; Validation: SS; Writing of original draft: MDS, Writing, reviewing, and editing: MDS, LH, SS.

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