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RESEARCH

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Effect of Mineralocorticoid receptor antagonism (MRA) on aldosterone-interleukin 6 axis in heart failure; second opinion. A case-control study

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Abstract

Background In cases of heart failure characterized by reduced ejection fraction (HFrEF), heightened levels of aldosterone negatively impact the progression of heart failure. Aldosterone exerts its influence through the activation of mineralocorticoid receptors, leading to the subsequent release of IL-6. Recently, the discovery of the role of mineralocorticoid receptor antagonism (MRA) in managing the progression of heart failure, particularly through its effect on IL-6, prompted its inclusion in the American College of Cardiology guidelines. In the years 2019 and 2021, studies elucidated the proinflammatory role of interleukin 6 in the cytokine storm associated with COVID-19, emphasizing the significance of IL-6 inhibitors in controlling this storm. Further research is required to examine the impact of mineralocorticoid receptor antagonism (MRA) on both aldosterone levels and IL-6 release in patients with HFrEF. Additionally, there is a need to assess the effectiveness of current MRA dosages in controlling heart failure with reduced ejection fraction.

Patients and methods A retrospective analysis was conducted on 108 patients with HFrEF diagnosed through echocardiography. The study covered the period from December 2021 to December 2022. All participants underwent blood tests for aldosterone and interleukin 6 using the ELISA test. The patients were categorized based on cardiac compensation status and the specific mineralocorticoid receptor antagonist (MRA) drug regimen they were on.

Results There was a notable rise in aldosterone levels and a reduction in serum IL6 observed in 30 patients with Acute Decompensated Heart Failure (ADHF) who were treated with Mineralocorticoid Receptor Antagonists (MRA), as compared to 30 patients with a similar diagnosis who did not receive MRA. Among 24 patients with compensated heart failure using MRA, there was a significant increase in aldosterone levels and a decrease in IL6, in contrast to 24 patients with compensated heart failure who were not on MRA therapy.

Conclusions In heart failure with reduced ejection fraction (HFrEF), inhibiting mineralocorticoid receptors leads to a reduction in pro-inflammatory IL-6. The action of Mineralocorticoid Receptor Antagonists (MRA) is deemed safe, well-tolerated, and cost-effective when compared to IL-6 inhibitors. There is a need to reevaluate the current MRA regimen with the objective of enhancing its efficacy for optimal reduction in IL-6 and effective control of heart failure progression.

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Background

Traditionally, the renin-angiotensin-aldosterone system (RAAS) has been conceptualized as a hormonal mechanism that regulates electrolyte balance and blood pressure. Angiotensin II, the primary effector peptide in the RAAS, induces vasoconstriction and stimulates the synthesis of aldosterone in the adrenal cortex. The effects of aldosterone are manifested through its binding to the mineralocorticoid receptor (MR). The MR is currently recognized as a receptor with widespread expression throughout the body. Although the MR's conventional actions predominantly occur in epithelial cells of the colon, kidney, and sweat glands, contributing to processes such as potassium secretion, sodium reabsorption, and extracellular volume regulation. Non-canonical functions of the MR may be triggered by inflammation or an altered microenvironment, resulting in fibrosis, hypertrophy, and remodeling [1].

Aldosterone is associated with several documented adverse effects on the cardiovascular system. It is suggested that aldosterone contributes to an increase in sympathetic activity within the heart muscle, a decrease in parasympathetic activity, and the initiation of an inflammatory response. Additionally, aldosterone is implicated in the failure of baroreceptors, causing direct harm to blood vessels, inducing endothelial dysfunction, compromising arterial elasticity, and elevating vascular tone. More recent research highlights the detrimental impact of aldosterone on endothelial function, specifically through oxidative stress [2, 12].

Aldosterone likely plays a crucial role in heart failure progression, especially evident in patients with chronic heart failure (HF) who exhibit elevated aldosterone levels associated with poorer outcomes. In the context of Acute Decompensated Heart Failure (ADHF), characterized by the abrupt or gradual onset of heart failure symptoms, most cases involve a deterioration of pre-existing chronic HF. However, around 15% to 20% of ADHF instances entail new diagnoses of HF with a left ventricular ejection fraction (LVEF) below 0.40 [3]. Notably, in patients experiencing acutely decompensated heart failure (ADHF), higher aldosterone levels are linked to unfavorable post-discharge outcomes, suggesting potential benefits from modifying the mineralocorticoid system during or immediately after hospitalization to improve overall results [3].

Since the identification in 1957 of a distinct category of synthetic steroids known as "spirolactones," which nullify the effects of aldosterone, various mineralocorticoid receptor antagonists (MRAs) have been developed. These blockers have been demonstrated to play a significant role in organ protection, particularly in the context of heart failure [4]. In the midst of the COVID-19 pandemic, the effectiveness of mineralocorticoid receptor blockers, such as spironolactone, has been established in managing cytokine storms [5]. The guidelines provided by the American College of Cardiology in 2017 for heart failure advise the use of mineralocorticoid receptor antagonists (MRAs), such as spironolactone, in patients with Heart Failure with Reduced Ejection Fraction (HFrEF) categorized as NYHA II-IV, as long as their creatinine clearance is over 30 mL/min and serum potassium levels remain below 5 mEq/L [5].

The utilization of mineralocorticoid receptor antagonists (MRAs) has shown effectiveness in enhancing outcomes and lowering mortality in cases of chronic heart failure (HF) characterized by reduced ejection fraction (HFrEF). The positive impact associated with MRAs is likely attributed to their ability to block excessive neurohormonal activation [1]. Spironolactone and eplerenone, both classified as mineralocorticoid receptor blockers, are recognized for their extended-term usage, characterized by relatively safe adverse profiles. However, the anti-inflammatory role of mineralocorticoid receptor blockers (MRAs) in heart failure has not been thoroughly and objectively examined in current usage. The current low dosages of MRAs in heart failure, for instance, 25-50 mg of spironolactone per day, are tailored to considerations such as hemodynamic stability, serum potassium levels, and renal function.

In the year 2017, the ATHENA-HF trial investigated the use of high-dose spironolactone in Acute Heart Failure (AHF), revealing good tolerability and safety. The study suggested the need for future research to explore higher dosages, especially for patients experiencing diuretic resistance [6]. Our hypothesis suggests the necessity for objective adjustment and monitoring of aldosterone antagonism in heart failure patients. There is a need for a measurable marker to guide the optimal dosing for maximal benefits. This marker should be tested in both compensated and decompensated heart failure patients.

In our retrospective study, our primary objective was to assess aldosterone and Interleukin 6 levels in patients with Heart Failure with Reduced Ejection Fraction (HFrEF), including those with Acute Decompensated Heart Failure (ADHF) and compensated heart failure, who were not receiving Mineralocorticoid Receptor Antagonists (MRA). Additionally, we aimed to investigate the impact of MRAs, specifically eplerenone and spironolactone, on both aldosterone and interleukin 6 levels in heart failure patients. Furthermore, we considered Interleukin 6 as a potential marker for gauging the severity and decompensation of heart failure. Additionally, we explored its utility as a metric for monitoring the effectiveness of MRAs at their current dosages.

Methods

This case-control study took place from December 2021 to December 2022, involving the selection of patients from both outpatient departments and the Intensive Care Unit (ICU) at ZAHRAA Hospital. The study aimed to compare specific cases with controls during this period.

Study population

Sample size calculation

One hundred thirty-three measurements are needed to have a confidence level of 95% that the real value is within ±8.5% of the measured/surveyed value. 133 participants were recruited with 5 blood samples that gave errors in readings. The remaining 128 participants were 108 patients and 20 control subjects.

All enrolled patients received a diagnosis of heart failure with reduced ejection fraction (HFrEF), confirmed through echocardiography indicating an ejection fraction (EF) below 50. Both plasma aldosterone level and interleukin-6 level were assessed in all groups using an enzyme-linked immunosorbent assay. Whole blood was obtained through venepuncture, and samples were promptly processed by centrifugation at 3000g for 15 minutes. Serum and plasma fractions were then aliquoted and stored at −80 °C until assay. The Siemens BN II Nephelometer was employed for IL-6 measurements, and the Aldosterone ELISA Assay Kit, utilizing enzyme immunoassay, quantitatively determined aldosterone levels in human serum and plasma (Aldosterone ELISA Assay Kit, SKU: ALD31-K01). Additionally, 20 age- and sex-matched healthy volunteers with no cardiac illnesses or relevant exclusion criteria were recruited as control group.

The study's goal was conveyed to all participants, ensuring confidentiality and anonymity. Informed consents were obtained from participants, who retained the right to withdraw at any point. In this study, individuals with a diagnosis or suspicion of primary hyper-aldosteronism, renal failure, or liver cirrhosis were excluded. Likewise, those with a diagnosis or suspicion of neoplasia, rheumatological disease, sepsis, morbid obesity, pneumonia, or any conditions that might interfere with IL-6 values were also excluded. HFrEF patients included in the study were categorized into four groups based on cardiac compensation and Mineralocorticoid Receptor Antagonist (MRA) blockade:

- Group I: Acute decompensated heart failure without aldosterone antagonism.
- Group II: Acute decompensated heart failure with eplerenone or spironolactone administered within the last week (50–100 spironolactone).
- Group III: Compensated heart failure without aldosterone antagonism.
- Group IV: Compensated heart failure with eplerenone or spironolactone taken for the last 3–6 months (25–50 spironolactone).

Statistical analysis

The data are presented as mean ± standard deviation (SD) or median values with an interquartile range (IQR) as applicable. Statistical analysis involved using either the Student's t-test or the Mann-Whitney U test for continuous data, depending on the distribution. Comparisons of variables across different groups, subgroups, and control values were conducted using either a paired Student's t-test or Wilcoxon's test. When appropriate, Pearson's or Spearman's correlation coefficients were employed to assess the relationship between two continuous variables. A *P*-value of less than 0.05 was considered statistically significant. The statistical software package Statistica was used for the analysis, along with Epitools for ROC (https://epitools.ausvet.com.au/roccurves) and (https://www.medcalc.org/calc/comparison_of_means.php).

Results

The distribution of patients across groups, categorized based on compensation and Mineralocorticoid Receptor Antagonist (MRA) therapy, is as follows:

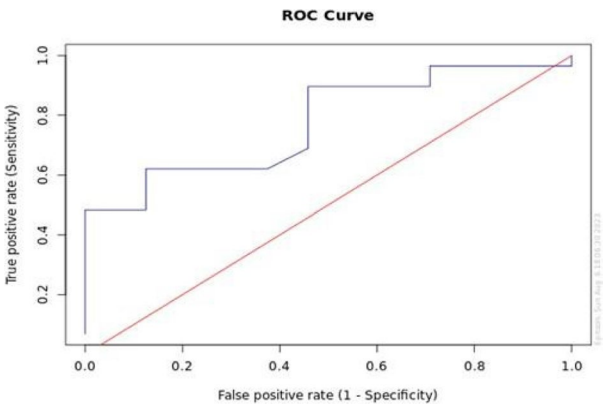
- Group 1: 30 patients with Acute Decompensated Heart Failure (ADHF) without MRA, New York Heart Association (NYHA) class 3-4.
- Group 2: 30 patients with ADHF with MRA, NYHA class 3-4.
- Group 3: 24 patients with compensated Heart Failure (HF) without MRA, NYHA class 2-3.
- Group 4: 24 patients with compensated HF with MRA, NYHA class 2-3.
- Control: 20 age- and sex-matched control subjects. The mean age ± SD is 49.4 ± 0.5, and 13 patients are male and 7 patients are female.

Among the total of 108 patients, the mean age ± SD is 46.4 ± 12.1, and 71 patients are male and 37 patients are female. Regarding the etiology of Heart Failure with Reduced Ejection Fraction (HFrEF), 26.9% have ischemic causes, 11.5% are diabetic, 17% are hypertensive, and 21% are cerebrovascular patients. All included patients have a reduced ejection fraction, with a mean ± SD of 28 ± 10.7%. Among HFrEF patients, 82.6% are maintained on ACE inhibitors, and 71% are on beta-blockers.

In the heart failure study population, aldosterone levels exhibit a significant elevation in acute

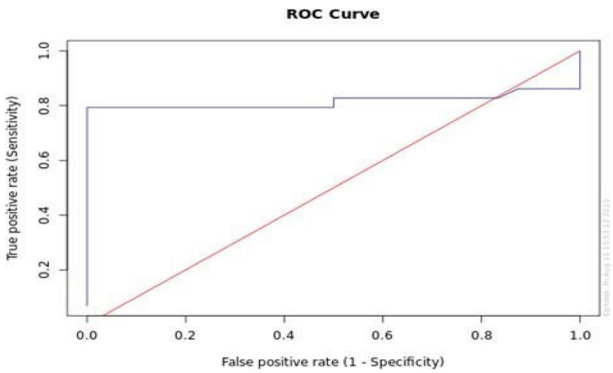
decompensated heart failure (ADHF) patients who are not using Mineralocorticoid Receptor Antagonists (MRA) (157.44 ± 89.78) compared to healthy subjects (56 ± 14.93), with a *p*-value less than 0.0001. Additionally, aldosterone levels are significantly higher in compensated heart failure patients than in healthy subjects (84.14 ± 38.26 vs. 56 ± 14.93), with a *p*-value of 0.0035. As well, IL-6 levels demonstrate a significant increase in acutely decompensated heart failure patients (17.27 ± 10.36) compared to healthy subjects (3.20 ± 0.52), with a *p*-value below 0.0001. Similarly, IL-6 levels are significantly higher in compensated heart failure patients (6.12 ± 0.91) compared to healthy subjects (3.20 ± 0.52), with a *p*-value less than 0.00001. In HFrEF patients without Mineralocorticoid Receptor Antagonists (MRA), a notable difference in aldosterone levels was observed between Acute Decompensated Heart Failure (ADHF) (157.44 ± 89.78) and compensated Heart Failure (HF) (84.1 ± 38.26), demonstrating statistical significance with a P value of 0.0005. Hence a positive correlation between Aldosterone level and cardiac decompensation.

The aldosterone cutoff value of 126 demonstrates high specificity at 0.833 in distinguishing between Acute Decompensated Heart Failure (ADHF) and compensated Heart Failure (HF), with a targeted specificity of 0.8. The specificity, with a 95% confidence level (CL), ranges from 0.641 to 0.933. The sensitivity is 0.621, with a sensitivity (95% CL) ranging from 0.44 to 0.773. The Receiver Operating Characteristic (ROC) curve analysis yielded an area under the curve (AUC) of 0.776, with a 95% confidence interval (CI) for AUC between 0.65 and 0.902.



ROC curve aldosterone in ADHF vs Comp HF

Furthermore, a significant difference in IL-6 levels was observed between Acute Decompensated Heart Failure (ADHF) (17.27 ± 10.36) and compensated Heart Failure (HF) (6.12 ± 0.91) with a P value less than 0.0001. The IL-6 cutoff of 7.9 exhibits a specificity of 0.95 in discriminating between ADHF and compensated HF, with a 95% confidence level (CL) ranging from 0.862 to 1. The sensitivity is 0.793, and its 95% CL ranges from 0.616 to 0.902. The area under the curve (AUC) is 0.815, with a 95% CI for AUC ranging from 0.678 to 0.953.



ROC IL6 in ADHF vs compensated HF

Conducting dual parallel testing of Aldosterone and IL-6 enhances the sensitivity to 0.92. In contrast, when performed in series, it increases specificity to 0.99 in discriminating between decompensated and compensated Heart Failure. The elevated levels of both aldosterone and interleukin 6 in acute decompensated heart failure patients who are not using mineralocorticoid receptor blockers, compared to compensated heart failure patients without these blockers, imply a potential correlation between aldosterone and IL-6 and the occurrence of cardiac decompensation.

In our study, a robust positive correlation was observed between aldosterone and IL-6 in Acute Decompensated Heart Failure (ADHF) patients not using Mineralocorticoid Receptor Antagonists (MRA) (r = 0.7694, $P < 0.00001$). Additionally, a moderate positive correlation was found between aldosterone and IL-6 in compensated HFrEF patients not using MRA (r = 0.5976), with a *P*-value of 0.002. When MRA was used, ADHF patients exhibited a statistically significant further increase in aldosterone levels (273.95 ± 175.69) compared to healthy individuals (56 ± 14.93), with a *p*-value less than 0.0001. Similarly, in patients with compensated Heart Failure (HF), aldosterone levels rose to (132.87 ± 82.16) versus (56 ± 14.93) controls, with a *p*-value of 0.0002. With MRA usage, although ADHF patients experienced a reduction in interleukin 6 levels (12.09 ± 5.19), IL-6 remained significantly higher than in healthy controls (3.20 ± 0.52) with a *P*-value less than 0.0001. Additionally, interleukin 6 in compensated HF patients decreased to 4.53 ± 0.49, still showing a statistically significant

Table 1 Presents the disparity in aldosterone and interleukin 6 levels between the primary groups and the control group

	HFrEF without MRA		HFrEF on MRA		Control
	ADHF	Compensated HF	ADHF	Compensated HF	
Serum aldosterone	157.44+/-89.78	84.14+/-38.26	273.95+/-175.69	132.87+/-82.16	56+/-14.93
P value	< 0.0001	= 0.0035	< 0.0001	= 0.0002	
Serum interleukin	17.27+/-10.36	6.12+/-0.91	12.09+/-5.19	4.53+/- 0.49	3.20+/-0.52
P value	< 0.0001	<0.00001	*P* < 0.0001	<0.0001	

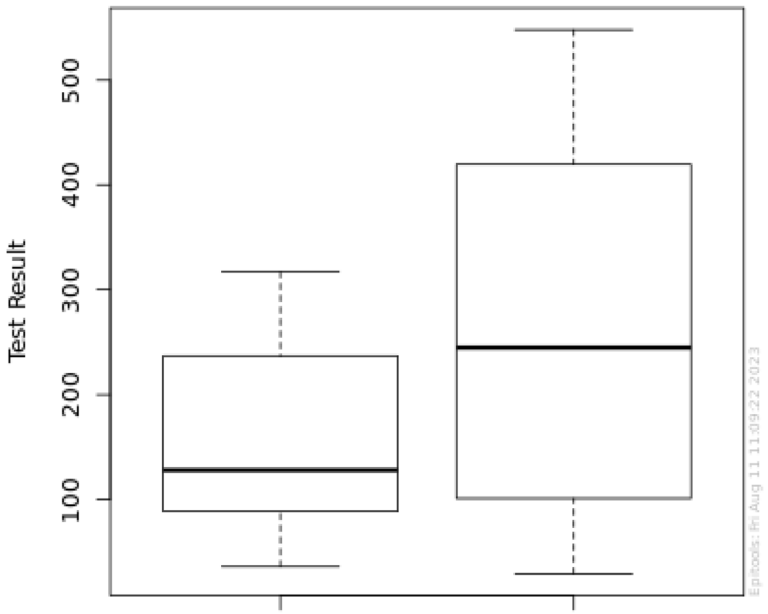


Fig. 1 Comparison between patients of ADHF(acute decompensated heart failure) not using MRA &ADHF(acute decompensated heart failure) Using MRA In Aldosterone Level

difference compared to healthy controls (3.20 ± 0.52) with a *P*-value less than 0.0001.

Table 1 provides a summary of the differences between the main groups in comparison to the control group concerning aldosterone and interleukin 6 levels.

Among patients with Acute Decompensated Heart Failure (ADHF), a comparison of aldosterone levels without Mineralocorticoid Receptor Antagonists (MRA) (157.44 ± 89.78) versus with MRA (273.95 ± 175.69) revealed a significant increase in the MRA group (p-value = 0.002) (Fig. 1). On the other hand, ADHF patients using MRA showed a significantly lower level of IL-6 (12.09 ± 5.19) compared to those without MRA (17.27 ± 10.36) with a p-value of 0.0174 (Fig. 2).

In the compensated Heart Failure (HF) groups, a comparison of aldosterone levels without MRA (84.14 ± 38.26) versus with MRA (132.87 ± 82.16) revealed a significant increase in the MRA group (P = 0.01) (Fig. 3). Regarding IL-6 levels, the comparison between compensated HF without MRA (6.12 ± 0.91) and the group using MRA (4.53 ± 0.49) revealed a significantly lower level of IL-6 with MRA (P < 0.0001) (Fig. 4).

Table 2 provides a summary of the impact of Mineralocorticoid Receptor Antagonists (MRA) on heart failure patients, specifically in terms of serum aldosterone and interleukin-6 (IL-6).

An aldosterone cutoff value of 548 demonstrates a specificity of 0.933 in distinguishing between Acute Decompensated Heart Failure (ADHF) and ADHF using Mineralocorticoid Receptor Antagonists (MRA). Additionally, the highest sensitivity in discriminating between both groups is associated with an aldosterone value of 35.95. The Area Under Curve (AUC) is 0.662, with a 95% confidence interval (CI) for AUC ranging from 0.515 to 0.809. For interleukin-6 (IL-6), a cutoff value of 22 exhibits the highest specificity in discriminating between ADHF and ADHF using MRA. The highest sensitivity in distinguishing ADHF versus ADHF using MRA is related

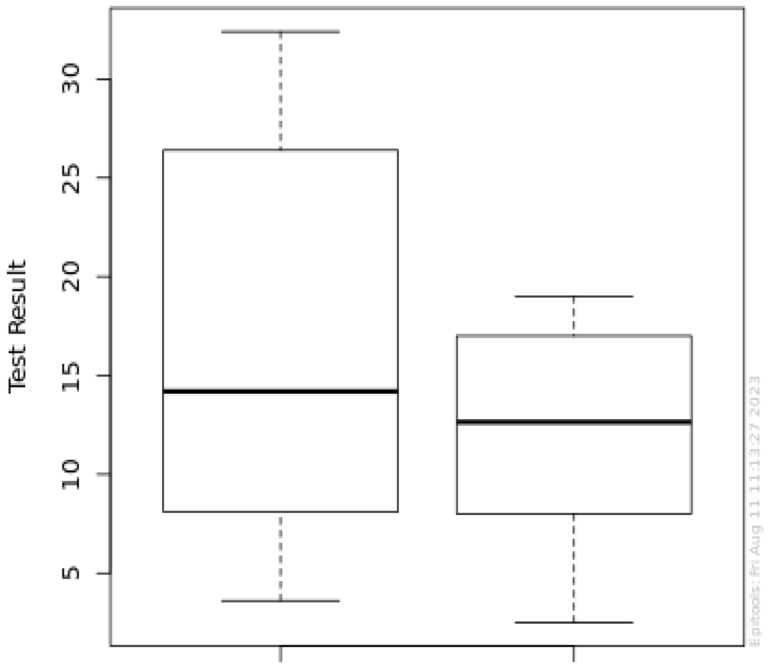


Fig. 2 Comparison between patients of ADHF(acute decompensated heart failure) not using MRA& patients of ADHF Using MRA In IL6 level

to a value of 3.6. The AUC is 0.616, with a 95% CI for AUC ranging from 0.464 to 0.768.

An aldosterone cutoff value of 249 demonstrates the highest specificity (0.917) in distinguishing between Compensated Heart Failure (Comp HF) with Mineralocorticoid Receptor Antagonists (MRA) and Comp HF. The highest sensitivity in discriminating between Comp HF and Comp HF using MRA is associated with an aldosterone value of 37. The Area Under Curve (AUC) is 0.655, with a 95% confidence interval (CI) for AUC ranging from 0.486 to 0.823. For interleukin-6 (IL-6), a cutoff value of 6.88 exhibits the highest specificity in discriminating between Comp HF and Comp HF using MRA, with a sensitivity related to an IL-6 value of 5.0. The AUC has a 95% CI ranging from 0.891 to 1.

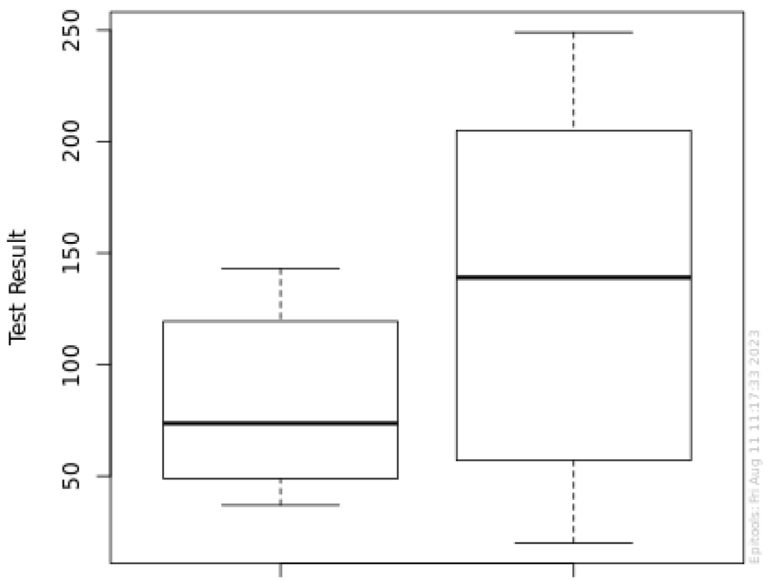


Fig. 3 Comparison Between Patients of Compensated HF not using MRA and patients of compensated HF using MRA in aldosterone level

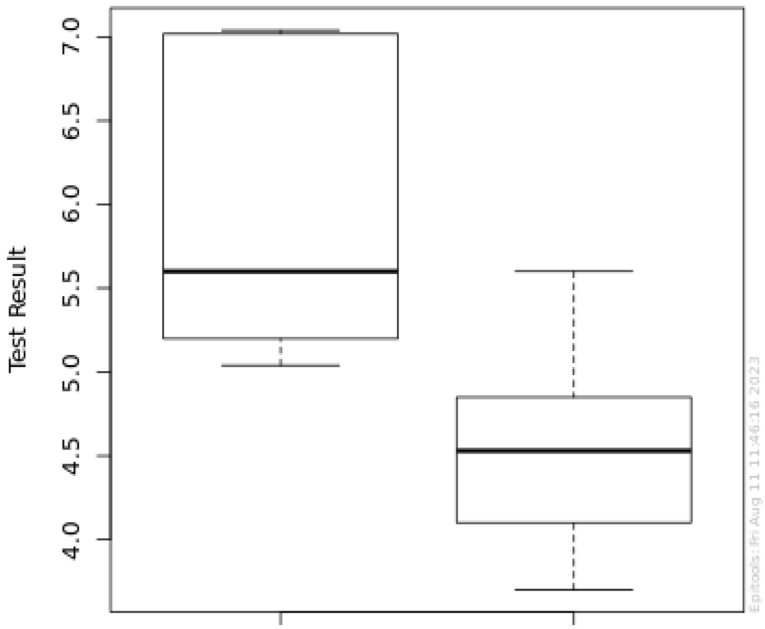


Fig. 4 Comparison between patients of Compensated HF not using MRA and patients of compensated HF using MRA in IL6 level

Discussion

Aldosterone exerts proinflammatory effects through the activation of mineralocorticoid receptors (MR) and subsequent release of interleukin 6 (IL-6). The utilization of MR antagonism has the potential to regulate these inflammatory effects. In the context of COVID-19, the focus has shifted towards the emerging role of IL-6 and its suppression in managing cytokine storms, albeit facing challenges related to cost and accessibility for all patients [7]. The control of interleukin 6 secretion through the antagonism of mineralocorticoid receptors is a promising, cost-effective, and relatively safe approach with a low adverse profile.

The evidence supporting the contribution of systemic inflammation to the pathophysiology of heart failure is emphasized by our study results. Aldosterone and IL-6 exhibit good sensitivity and specificity in discriminating between Acute Decompensated Heart Failure (ADHF) and compensated heart failure. Therefore, aldosterone and IL-6 can serve as markers for assessing the severity of cardiac decompensation. These findings align with the results of Resic N et al. (2018) and Su J-H et al. (2021) [2, 8]. This data is consistent with the findings of Parissis J.T. et al. (2004) [9]. Additionally, Minguell ER (2004) observed a progressive increase in IL-6 values as heart failure symptoms worsened, correlating with the deterioration of NYHA functional class [10]. In heart failure patients; it is proved that high IL-6 level is a marker for poor prognosis and associated with greater mortality [11].

In our study, a robust positive correlation was identified between aldosterone and IL-6 in Acute Decompensated Heart Failure (ADHF) patients (not using MRA) with a *P*-value less than 0.00001. While, among compensated Heart Failure with reduced ejection fraction (HFrEF) patients (not using MRA), a moderate positive

Table 2 Outlines the impact of Mineralocorticoid Receptor Antagonists (MRA) on heart failure patients, specifically in terms of serum aldosterone and IL-6 levels

	ADHF NYHA 3-4	**ADHF using MRA (e.g spironolactone 50-100mg/d) NYHA 3-4**	***P* value**	**Compensated HF NYHA 2-3**	**Compensated HF using MRA(e.g spironolactone 25-50mg/d) NYHA 2-3**	***P* value**
Serum aldosterone	**157.44+/-89.78**	273.95+/-175.69	*p*=0.002	**84.14+/-38.26**	132.87+/-82.16	*P* = 0.01
Serum interleukin 6	17.27+/-10.36	12.09+/-5.19	0.0174	6.12+/-0.91	4.53+/-0.49	<0.0001

correlation between aldosterone and IL-6 was observed, with a *P*-value of 0.002. This positive correlation is likely attributable to mineralocorticoid receptor-dependent IL-6 release in heart failure. Among patients with ADHF using MRA, aldosterone levels were further elevated compared to the control group, displaying a statistically significant difference. Similarly, compensated heart failure patients using MRA exhibited statistically significant higher aldosterone levels. These findings align with the results of Ferreira JP et al. (2014) [3].

Our results support the notion that MRA administration in both ADHF and compensated HF groups led to a significant reduction of IL-6 levels, approximately by 30%, although IL-6 remained significantly higher than the healthy control level. Among study patients using MRA, the correlation between aldosterone and IL-6 decreased in ADHF and was lost in compensated HFrEF. This finding can be explained by the increase in aldosterone levels combined with a decrease in IL-6 levels when using MRA.

Conclusions

- The administration of MRAs in heart failure yields a reduction in proinflammatory IL-6, thereby mitigating the adverse effects associated with secondary hyperaldosteronism and significantly enhancing the clinical performance of heart failure patients.
- The demonstrated efficacy of current MRA regimens in managing the adverse effects of aldosterone and IL-6 levels in heart failure patients emphasizes their importance. However, achieving normalization of the inflammatory marker IL-6 remains a challenging endeavor and far from optimum.
- IL-6 levels can function as a valuable marker for assessing the severity of heart failure and decompensation. even in the presence of Mineralocorticoid Receptor Antagonists (MRA), with an inverse relationship to MRA dosing.
- Guided by interleukin-6 levels and aspiring to approach near-normal values, the prospect of further escalating current MRA doses for heart failure patients to the highest-tolerated levels is considered.
- The validation and confirmation of our findings warrant a comprehensive large cohort study.

Abbreviations

IL	Interleukin
MRA	Mineralocorticoid receptor antagonism
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
AId	Aldosterone
IL 6	Interleukin 6
CHF	Congestive heart failure
RA	Rheumatoid arthritis
ADHF	Acute decompensated heart failure
MR	Mineralocorticoid receptor
ACE	Angiotensin converting enzyme
ARBs	Angiotensin receptor blockers
GM-CSF	Granulocyte-macrophage colony stimulating factor
RAAS	Renin–angiotensin–aldosterone system
Comp HF	Compensated heart failure

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Authors' contributions
Dr H. Elsawi the corresponding author; performs writing, collecting data, statistics and analysis. Dr S. Zidan ; co-author shares data gathering, statistical analysis and citation handling. Dr A. Elborolosy: co-author shares in protocol design; data statistical analysis and citation handling.

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Availability of data and materials
Better to be open access

Declarations

Ethics approval and consent to participate
Approvals for undertaking study from Badr university ethical committee; BUC. In addition, aim of study to be clarified to all participants and confidentiality and anonymity to be assured through coding data. Oral informed consent is to be taken from patients. Participants can withdraw at any time without any rationale.

Consent for publication
I agree to publish our work; being corresponding author of the topic

Competing interests
Being corresponding author of manuscript, i declare no competing interests.

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