ORIGINAL ARTICLE

Association between multivitamin supplementation and mortality among patients with Ebola virus disease: An international multisite cohort study

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ABSTRACT

Introduction: Micronutrient supplementation is recommended in Ebola Virus Disease (EVD) care; however, there is limited data on its therapeutic effects.

Methods: This retrospective cohort study included patients with EVD admitted to five Ebola Treatment Units (ETU) in Sierra Leone and Liberia during September 2014 to December 2015. A uniform protocol was used to guide ETU care, however, due to supply limitations, only a subset of patients received multivitamins. Data on demographics, clinical characteristics, and laboratory testing was collected. The outcome of interest was facility-based mortality and the primary predictor was multivitamin supplementation initiated within 48 h of admission. The multivitamin formulations included: thiamine, riboflavin, niacin and vitamins A, C, and D₃. Propensity score models (PSM) were used to match patients based on covariates associated with multivitamin administration and mortality. Mortality between cases treated and untreated within 48 h of admission were compared using generalized estimating equations to calculate relative risk with bootstrap methods employed to assess statistical significance.

Results: There were 424 patients with EVD who had sufficient treatment data for analysis, of which 261 (61.6%) had daily multivitamins initiated within 48 h of admission. The mean age of the cohort was 30.5 years and 59.4% were female. In the propensity score matched analysis, mortality was 53.5% among patients receiving multivitamins and 66.2% among patients not receiving multivitamins, resulting in a relative risk for mortality of 0.81 (p = 0.03) for patients receiving multivitamins.

Conclusion: Early multivitamin supplementation was associated with lower overall mortality. Further research on the impact of micronutrient supplementation in EVD is warranted.

African relevance

- Outbreaks of Ebola Virus Disease are common in sub-Saharan Africa
- Despite nearly two dozen outbreaks, little data has been collected to date on the effectiveness of various supportive care measures for Ebola Virus Disease
- The results of this study can be used to improve care for patients with Ebola Virus Disease in the current outbreak in DRC as well as future outbreaks

Introduction

The 2014–16 Ebola virus disease (EVD) epidemic in West Africa resulted in > 28,000 infections and over 11,000 deaths, with populations in Liberia, Sierra Leone, and Guinea most affected [1]. Among patients treated outside of Africa during the epidemic, mortality was

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18.5% [2], approximately half that of the lowest reported mortality from any of the Ebola treatment units (ETUs) in Africa [3–7]. Patients with EVD cared for in high-income countries (HICs) received extensive supportive care measures, many of which were not consistently available in the African setting [8]. Although the impacts of supportive care strategies on EVD mortality in low-resource settings are potentially promising, the roles of specific components of that supportive care remain largely unstudied.

Micronutrients are a common component of supportive care in EVD [2,3,5,9–13], and international guidelines call for supplementation when micronutrient deficiencies are present [14,15]. This includes the use of multivitamins, which have been associated with clinical improvement in other infectious diseases, such as tuberculosis, dengue and HIV [16–19]. Multivitamins also provide cofactors that have been shown to have clinical benefits in sepsis [20–23]. Furthermore, research on vitamin supplementation demonstrates the greatest benefits in populations with a low baseline nutritional status [24], such as in sub-Saharan Africa [25,26], This prior evidence suggest that the use of low-cost multivitamins could yield clinical benefits in patients with EVD; however, no data currently exists on the impact of multivitamin supplementation on patient-centered outcomes.

During the 2014–16 EVD epidemic, International Medical Corps (IMC) established and operated five ETUs in Liberia and Sierra Leone, which cared for 478 patients diagnosed with EVD. Clinical, epidemiologic, and laboratory data were gathered on most patients, resulting in a robust, multi-national database to investigate the roles of specific management strategies on patient outcomes [27]. This study evaluated the impact of early multivitamin supplementation on mortality among patients with EVD admitted to the five IMC ETUs.

Methods

This retrospective multisite cohort study utilized data collected at five ETUs operated by IMC between September 15, 2014 and December 31, 2015 in Liberia and Sierra Leone [27]. The ETUs were setup in areas identified as needing access to care in the affected communities distinct from pre-existing health centers and were comprised of organized triage, treatment and staff areas and housed all supplies needed to care for patients in the outbreak setting. ETUs at Makeni, Lunsar and Margibi were standard, white tents, while ETUs at Kambia and Bong were constructed with aluminum roofs, with either brick (Kambia) or blue-tarp walls (Bong) [28]. The Sierra Leone Ethics and Scientific Review Committee and the University of Liberia and Rhode Island Hospital Institutional Review Boards provided ethical approval for this study.

All patients admitted to the five study ETUs with a final diagnosis of EVD during the months of operation were eligible for inclusion. Patients who were deceased at time of arrival, confirmed to be negative for EVD by real-time reverse transcriptase-polymerase chain reaction (RT-PCR) testing, or missing data on multivitamin treatment were excluded from analysis.

All admitted patients were treated by trained response providers using standardized guidelines, developed by IMC in consultation with local health authorities (Appendix) [14,29]. The guidelines included daily supplementation with multivitamins for all patients. However, due to variations in the availability of multivitamins over the course of the epidemic, actual care varied. Two primary multivitamin formulations were used in the IMC ETUs, based on availability. The first, manufactured by Medopharm Private Limited, Chennai, India, included Vitamin A (2500 IU), B1 (1 mg), B2 (0.5 mg), B3 (7.5 mg), C (15 mg), and D3 (300 IU), while the second, manufactured by CSPC Ouyi Pharmaceutical Co, Shijiazhuang, China, included Vitamin A (800 IU), B1 (0.5 mg), B2 (0.5 mg), B3 (7.5 mg), and D3 (200 IU). In addition to the multivitamins, the IMC guidelines also recommended Vitamin A (1000 retinol units on Day 1 and 2) and Vitamin C (500 mg three times daily) supplementation, though actual care varied based on supply availability.

Admittance to the EVD-confirmed ward of the ETUs required positive RT-PCR laboratory confirmation. Ebola virus RT-PCR cycle threshold (CT) values, which are inversely proportional to viral load, were obtained from the United States Naval Medical Research Center Mobile Laboratory for ETUs in Liberia and Public Health England and the Nigerian/European Mobile Laboratory for ETUs in Sierra Leone using previously published procedures [30]. Malaria testing, when performed, utilized the commercially available BinaxNow™ rapid diagnostic test (RDT), which identifies four *Plasmodium* species: Falciparum, Malariae, Vivax and Ovale.

As reported previously, trained providers collected data on demographics and baseline clinical signs/symptoms at triage on standardized forms [27]. Clinical characteristics and treatment data were recorded one to six times daily (median 3 times daily) on all admitted patients based on human resource availability using standardized forms, while final disposition and diagnosis were recorded on standardized discharge forms, as described previously [27,30]. All data forms were digitized and filed into a unified relational electronic database [27]. Data quality was measured using Lot Quality Assurance Sampling, which demonstrated 99% consistency with the source records [27,31].

Statistical analyses were undertaken using R version 3.3.3 [32]. Descriptive analyses were performed for all variables using frequencies with percentages, medians with interquartile ranges (IQR), or means with standard deviations (SD) as appropriate.

The outcome of interest was observed mortality during ETU care. Due to the high immediate post-admission mortality risks documented in the study ETUs [30], and the resulting potential survivor bias, the primary predictor variable utilized was early oral multivitamin treatment, defined as initiation within 48 h of admission. Multivitamin treatment was coded as dichotomous in the primary analysis. Time of multivitamin initiation and duration of treatment were summarized. Univariate analyses compared demographic and clinical characteristics between groups treated and not treated with multivitamins and also between patients suffering mortality and those who survived, using Pearson X^2 or Fisher's exact tests for categorical variables and by Mann-Whitney or *t*-tests for continuous variables, as appropriate.

Propensity score development and modeling

To control for confounding, a propensity score model (PSM) was used to match and compare patients treated and not treated with multivitamins during the first 48 h of ETU care [33]. Variables were chosen for inclusion in the PSM based on their univariate relationship to multivitamin exposure or survival in either the study cohort or prior literature [33].

Variables of gender, abnormal bleeding, malaria RDT results and triage CT values were modeled as categorical, while age was modeled utilizing a cubic spline to control for the known quadratic relationship between age and survival in EVD [30]. After fitting the PSM, a common support interval approach to prevent over-extrapolation was used in which all observations, with a probability of receiving treatment less than the minimum in the treated cohort and greater than the maximum in the control cohort, were filtered out [34]. After filtering for the common support interval, two patients were removed. Each multivitamin treated patient was matched to an untreated patient with the nearest propensity score and exact CT value and malaria testing results (due to the high correlation of those factors with the outcome of interest) [5,30,35,36]. Matching was done with replacement for the untreated cohort. Covariate balance was assessed before and after matching based on the standardized bias, to ensure balance between treatment and control cohorts. Following 1:1 matching, with 76 unique controls, the probability of mortality between cases treated and not treated with multivitamins was assessed. Mortality outcomes between cases treated and not treated with multivitamins were compared using propensity-matched generalized estimating equations (GEE) to calculate relative risks (RR). Bootstrap methods with 1000 iterations were

used to calculate p-values and characterize statistically significant differences between groups.

Since demographic and clinical data were available for all included patients, only laboratory data was missing. As laboratory data was not missing at random (patients who died were more likely to lack laboratory results), multiple imputation was not utilized. Instead, CT values were categorized as: >22 (low viral load), ≤22 (high viral load), and missing, to prevent the introduction of bias (cut-points were based on those used previously in the literature) [37]. Similarly, results for malaria RDTs were coded as positive, negative or missing.

Three sensitivity analyses were performed using propensity-matched generalized estimating equations as described in the primary analysis. The first compared mortality outcomes between patients treated with vitamin A without multivitamins to those treated with vitamin A and multivitamins. The second compared those treated with vitamin C without multivitamins to those treated with vitamin C and multivitamins. The final sensitivity analysis assessed mortality between those treated and not treated with early multivitamin supplementation and matched on a broad selection of pharmacologic agents which included paracetamol, omeprazole, vitamin A, vitamin C, Coartem, and cefixime, as well as the other covariates used in the primary model. In all sensitivity analyses, covariate balance was assessed before and after matching based on the standardized bias.

Results

In the overall population, 478 patients with EVD presented to the study ETUs during operation, of which 424 had sufficient data for analysis (Fig. 1). The mean age was 30.5 (SD: 18.7) years and 59.4% were female. The median duration of care was 8 (IQR: 5, 13) days. There was larger proportion of patients from Sierra Leone ETUs versus those from those operated in Liberia. Table 1 provides data on the proportion of patients who developed clinical signs and symptoms during ETU care. CT values were available for 281 patients, of which 159 (37.5%) had a high viral load (CT value ≤ 22).

During ETU care 313 (73.8%) patients were treated with multivitamins among which 261 (61.6%) patients had daily multivitamins initiated during the first 48 h of care. Median length of treatment with multivitamins for all cases was 5 (IQR: 3, 10) days. Frequency distributions for the time to initiation and duration of treatment with multivitamins are shown in Fig. 2. Patients receiving multivitamins during the first 48 h were significantly more likely to be female and have low CT values, and were significantly less likely to have symptoms/signs of anorexia, bleeding, confusion and fever during ETU care (Table 2). Co-treatment within 48 h of care with multivitamin and vitamin A or multivitamin and vitamin C occurred in 248 (58.9%) and

Table 1
Characteristics overall cohort.

	n (%) or mean (±SD)
Age	30.5 (±18.7)
Sex	
Female	253 (59.4)
Male	171 (40.3)
Country	
Liberia	134 (31.6%)
Sierra Leone	290 (68.4%)
CT values	
High viral load	159 (37.5)
Low viral load	122 (28.8)
Missing	143 (33.7)
Clinical characteristics	
Anorexia	342 (80.7)
Any bleeding	198 (46.9)
Coma	42 (9.9)
Confusion	56 (13.4)
Diarrhea	363 (85.6)
Dysphagia	248 (58.7)
Dyspnea	204 (48.3)
Fever	325 (76.7)
Stomach pain	326 (76.9)
Vomiting	325 (76.7)

SD = Standard Deviation, CT = Cycle Threshold.

230 (54.2%) patients, respectively.

Overall, 244 (57.5%) patients died during ETU care. As reported previously, there were no significant differences in mortality outcomes between the five ETU sites [30]. Viral load on admission was strongly correlated with mortality: among patients who died, 44.7% of cases had a CT value ≤ 22 while only 16.8% of cases had a CT value > 22 (p < 0.001). Patients who died were significantly more likely to have developed bleeding, diarrhea, dysphagia and dyspnea during ETU care (Table 3).

Observed mortality was 53.6% among patients treated with multivitamins within 48 h of admission and 63.8% among patients not treated within 48 h of admission. For patients who died, median survival time was 4 (IQR: 2, 6) days among cases not receiving multivitamins within 48 h of ETU admission and 5 (IQR: 4, 7) days among those receiving multivitamins.

Propensity matched analysis

Propensity matching achieved covariate balance among all predictors associated with either multivitamin administration, mortality, or both (Fig. 3), allowing for a fair comparison between groups. In the propensity score matched analysis, mortality was 53.5% among patients receiving multivitamins and 66.2% among patients not receiving multivitamins, with a risk ratio (RR) of 0.81 (p = 0.03) for mortality when multivitamin treatment was initiated within the first 48 h of ETU care.

In a propensity score matched analysis comparing patients receiving both vitamin A and early multivitamin supplementation to patients receiving vitamin A without early multivitamins, there was no significant difference in the relative risk of mortality between treatment groups (RR = 0.92, p = 0.70). In a separate vitamin C sensitivity analysis, significantly lower mortality risk was observed in patients treated with both early multivitamins and vitamin C as compared to those receiving vitamin C and no early multivitamins (RR = 0.64, p < 0.001). In a third sensitivity analysis matching on a broad selection of medications to control for confounding by other treatments received, patients treated with early multivitamins as compared to those not treated still had a reduced risk of mortality (RR = 0.74, p = 0.03).
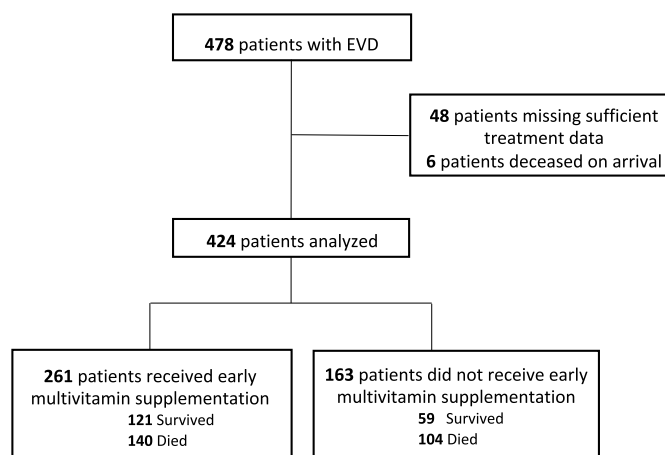
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┌─────────────────────────────┐
│ 478 patients with EVD       │
└─────────────────────────────┘
           │
           │        ┌─────────────────────────────────┐
           ├────────│ 48 patients missing sufficient  │
           │        │ treatment data                  │
           │        │ 6 patients deceased on arrival  │
           │        └─────────────────────────────────┘
           │
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│ 424 patients analyzed       │
└─────────────────────────────┘
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     ┌─────┴───────────────────┐
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│ 261 patients       │  │ 163 patients did   │
│ received early     │  │ not receive early  │
│ multivitamin       │  │ multivitamin       │
│ supplementation    │  │ supplementation    │
│ 121 Survived       │  │ 59  Survived       │
│ 140 Died           │  │ 104 Died           │
└────────────────────┘  └────────────────────┘
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Fig. 1. Study population.

A. Frequencies of Treatment Initiation Days
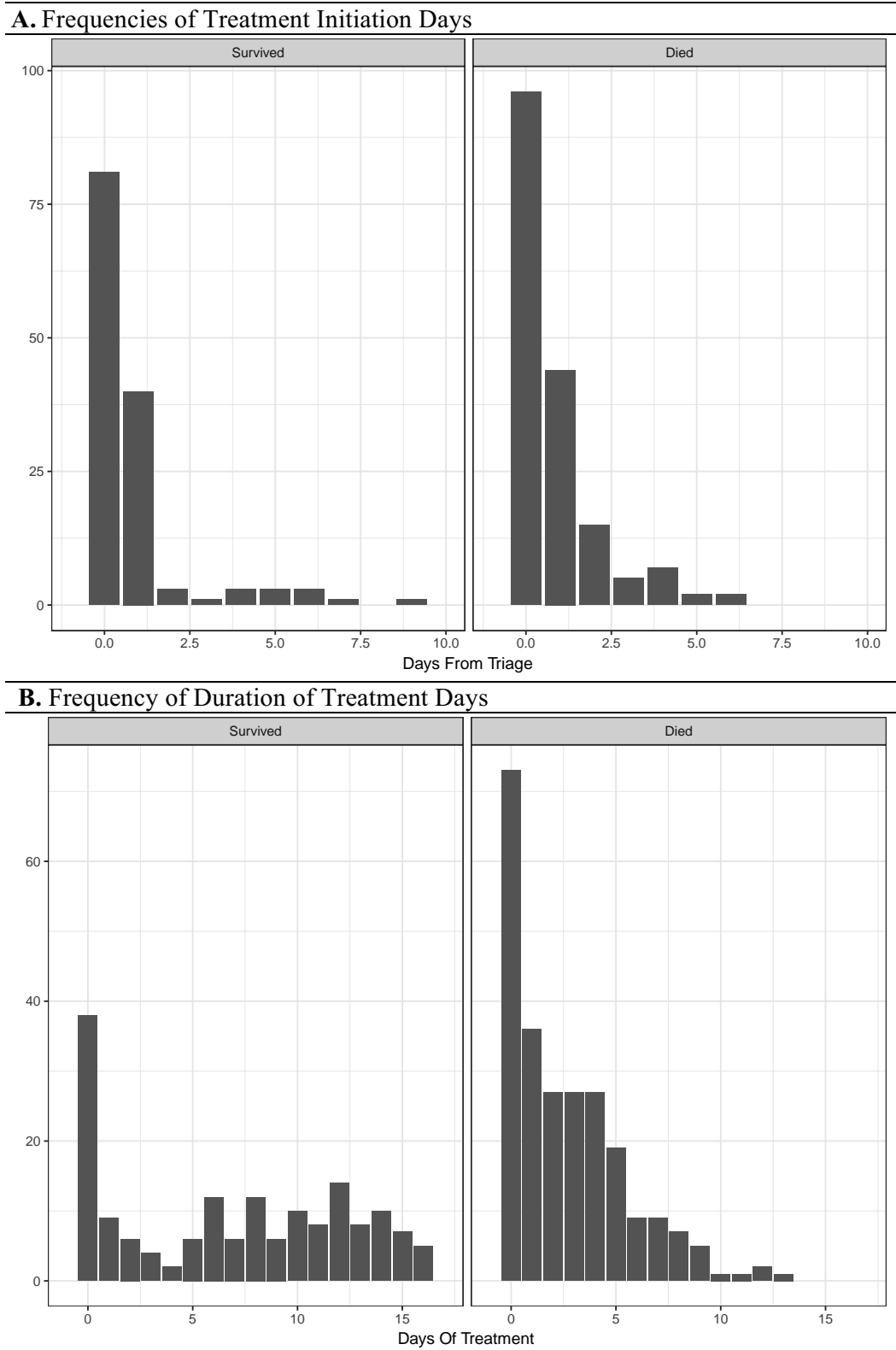
B. Frequency of Duration of Treatment Days

Fig. 2. Multivitamin treatment initiation and duration times stratified by outcome.

Discussion

The current report is the first to demonstrate the clinical impact of multivitamin supplementation on clinical outcomes in patients with EVD in a resource-limited setting. The results demonstrate that patients with EVD who were treated with early oral multivitamin supplementation had lower facility-based mortality than those who were not treated with early oral multivitamin supplementation, even after adjusting for potential confounders using propensity score matching. Given these findings, in conjunction with the low-cost of multivitamins, this supportive therapy should be considered for use in future EVD outbreaks.

Table 2
Patient characteristics stratified by treatment status.

	Multivitamin (−) (n = 163) n (%) or mean (±SD)	Multivitamin (+) (n = 261) n (%) or mean (±SD)	p value
Age	31 (±18)	30.2 (±19.2)	0.693
Sex			
Female	85 (52.1)	168 (64.4)	0.014
Male	78 (47.9)	93 (35.6)	
CT values			
High viral load	33 (20.2)	126 (48.3)	<0.001
Low viral load	49 (30.1)	73 (28.0)	
Missing results	81 (49.7)	62 (23.8)	
Clinical characteristics			
Anorexia	119 (73.6)	163 (62.5)	0.015
Any bleeding	60 (37.4)	61 (23.4)	0.003
Coma	1 (1.2)	3 (1.5)	0.791
Confusion	16 (10.4)	10 (4.2)	0.022
Diarrhea	112 (69.3)	185 (70.9)	0.735
Dysphagia	73 (44.8)	97 (37.5)	0.143
Dyspnea	57 (35)	78 (29.9)	0.280
Fever	138 (84.7)	182 (70.1)	0.000
Stomach pain	104 (64.4)	159 (61.3)	0.519
Vomiting	102 (62.6)	151 (58.2)	0.374

SD = Standard Deviation, CT = Cycle Threshold.

Table 3
Patient characteristics stratified by mortality status.

	Discharged alive (n = 180) n (%) or mean (±SD)	Suffered mortality (n = 244) n (%) or mean (±SD)	p value
Age	28.7 (±15.3)	31.8 (+20.8)	0.080
Sex			
Female	108 (60)	145 (59.4)	0.906
Male	72 (40)	99 (40.6)	
CT values			
High viral load	50 (27.8)	109 (44.7)	<0.001
Low viral load	81 (45.0)	41 (16.8)	
Missing results	49 (27.2)	94 (38.5)	
Clinical characteristics			
Anorexia	86 (47.8)	119 (48.8)	0.840
Any bleeding	32 (17.8)	61 (25.4)	0.057
Coma	0 (0)	1 (0.8)	0.158
Confusion	5 (3.3)	13 (5.7)	0.231
Diarrhea	93 (51.7)	152 (62.3)	0.029
Dysphagia	43 (24.4)	90 (36.9)	0.006
Dyspnea	39 (21.7)	80 (32.8)	0.010
Fever	133 (73.9)	183 (75.4)	0.723
Stomach pain	91 (50.6)	134 (55.3)	0.332
Vomiting	86 (48.3)	115 (47.5)	0.872

SD = Standard Deviation, CT = Cycle Threshold.

Although nutritional status impacts immune function and micronutrient supplementation is a common component of supportive care in EVD [2,3,5,9–13,38,39], there are no other published reports investigating the impacts of multivitamins in the treatment of EVD patients under outbreak conditions. However data from other infectious disease states provides support for the provision of multivitamins in EVD. Multivitamins have been associated with clinical improvement in the care of patients with tuberculosis and HIV [16–18]. A randomized, placebo-controlled trial conducted in Tanzania with multivitamins composed of vitamins B-complex, C, and E, found that HIV-infected pregnant women not on HIV treatment who received multivitamin supplementation had significantly improved immune responses, reduced HIV disease progression, and death [17]. An additional placebo-controlled trial utilizing micronutrient supplements (vitamins A, B-complex, C, E and selenium) found a significant reduction in TB

recurrence risk among HIV-negative patients [19]. Vitamin C has shown benefits in upper respiratory infections and severe pneumonias [16,40], and evidence also demonstrates that treatment with vitamins C is associated with improved hemodynamics and survival in severe sepsis [20], which has similar pathophysiology to EVD [21,22]. Vitamins D suppresses T-cell activation and genes involved in cell proliferation and differentiation; down-regulates the production of pro-inflammatory cytokines; and plays multiple roles in antimicrobial defense and immune regulation [41,42]. Given this body of evidence there is biological plausibility for the improved mortality observed in the current data among patients with EVD who received early multivitamin supplementation.

In sensitivity analysis controlling for a broad range of pharmacologic treatments, similar benefits were found with early multivitamin supplementation. In the sensitivity analyses evaluating patients also treated with vitamin C, the addition of multivitamins still resulted in significantly reduced mortality. In assessing the addition of multivitamins to patients already treated with vitamin A, however, there was no significant differences in mortality identified. This may indicate that vitamin A is a key micronutrient responsible for the improved outcomes observed, as the magnitude of the early multivitamin effect on mortality was mitigated, yet not fully negated, in the vitamin A sensitivity models. The potential benefits of vitamin A therapies in EVD are supported by prior literature on vitamin A showing that it is essential for innate and adaptive immunity – being integral in the maintenance of epithelial integrity and differentiation and function in cellular immune response [43–45]. Given the limited power to detect significant differences, these sensitivity analyses should be considered exploratory. However, they do highlight the need for further research pertaining to micronutrient supplementation in EVD care and suggest vitamin A should be an important focus of future studies.

The World Health Organization guidelines for viral hemorrhagic fever state that patients do not need micronutrient supplementation if adequate fortified nutrition is administered [14]. However, vitamin A is recommended for children under five years of age who have not received vitamin A supplementation in the past six months [14]. The Médecins Sans Frontières guidelines recommend supplementation only if micronutrient deficiency is present [15]. Given the high baseline prevalence of malnutrition and specifically micronutrient deficiencies that exist in sub-Saharan African populations [25,26], and particularly the west African populations that were most affected during the 2014–2016 outbreak [16,46,47], empiric treatment with multivitamins during outbreaks occurring in the African context is currently warranted, unless future research demonstrates harms or futility with such approaches.

This study must be interpreted with limitations. The multivitamin supplementation data were not drawn from patients who were randomized to either a treatment or a control allocation. Although a propensity score matched analysis was employed to control for confounding, it cannot control for unmeasured or missing variables. However, it should be noted that the decision to withhold multivitamins was based mostly on supply limitations, as they were a standard part of the clinical protocol at all five sites, reducing the likelihood of confounding by indication. Although rigorous data acquisition methods were used, which provided a high-quality database for analysis, there was some missing laboratory information for CT values and malaria RDT results. To minimize any bias derived from the missing laboratory data, the models were run such that cases were matched exactly on the status of those variables. Although less important from a programmatic and outbreak response perspective, the present data does not allow us to determine which specific components of the multivitamin supplementation accounted for the benefits observed. Future laboratory and clinical research would have utility in further investigating the biochemical mechanisms of micronutrient supplementation in reducing mortality for patients with EVD. Finally, all studied patients were treated at IMC facilities, which may threaten the
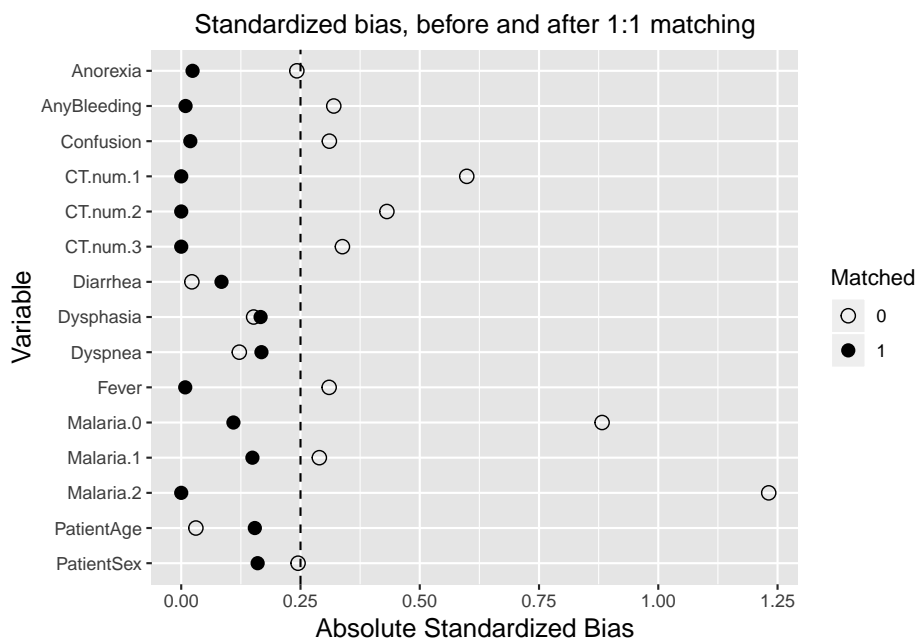
Standardized bias, before and after 1:1 matching

Fig. 3. Covariate balance among predictors before and after propensity score matching.

generalizability of the findings. However, as the IMC guidelines utilized to guide clinical care at all sites were based on other international guidelines in widespread use and the resource constraints experienced by IMC were common at most ETUs during the 2014–2016 epidemic, these data are likely generalizable to future EVD outbreaks in low-resource settings of sub-Saharan Africa.

Conclusion

The magnitude of the West Africa epidemic and the ongoing 2018–2019 outbreak in the Democratic Republic of Congo and Uganda [48], point-up the threats of EVD globally and the imperative need for advancement of understanding of pragmatic and impactful treatment strategies. The current data, which is derived from a large, multisite, epidemic population, is the first available on multivitamin supplementation in an outbreak setting from a high-risk population in Africa and demonstrates that early treatment resulted in lower overall mortality in adjusted analyses. Given these findings, in conjunction with the low-cost for supplementation, and the demonstrated safety of multivitamins in prior infectious disease research [49,50], supportive therapy with multivitamins should be further studied and considered for use in future EVD outbreaks occurring in populations with high burdens of nutritional deficiencies.

Dissemination of results

Results of this study were shared with the International Medical Corps team currently responding to the EVD outbreak in the Democratic Republic of Congo.

Authors' contribution

Authors contributed as follow to the conception or design of the work; the acquisition, analysis, or interpretation of data for the work; and drafting of the work, or revising it critically for important intellectual content: DY and ARA contributed 25% each; TL and ACL 10% each; SMP 15%; and JLP, DKC, SBK, MM, FS, MAS and LL 2% each. All authors approved the version to be published and agreed to be accountable for all aspects of the work.

Conflict of interest

The authors declare no conflict of interest. All authors had full access to all study data and had final responsibility for the decision to submit for publication. The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the views of International Medical Corps or any governmental bodies or academic organizations. This work was supported by the National Institutes of Health (NIH) National Institute of Allergy and Infectious Diseases [grant number R03AI132801]. The funding source had no involvement in the design or conduct of the study or the decision to submit for publication.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.afjem.2019.11.001. Additional data may be accessed through the Ebola Data Platform at https://www.iddo.org/research-themes/ebola.

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