Blunted Heart Rate Dip During Sleep and All-Cause Mortality

Iddo Z. Ben-Dov, MD; Jeremy D. Kark, MD; Drori Ben-Ishay, MD; Judith Mekler, MSc; Liorna Ben-Arie; Michael Bursztyn, MD

Background: Although it has been somewhat overlooked, resting heart rate is an established predictor of cardiovascular and noncardiovascular outcome. We assessed the determinants and mortality associations of heart rate measured during ambulatory blood pressure monitoring (ABPM) to evaluate its informativeness during activity and sleep.

Methods: We studied a cohort of 3957 patients aged 55±16 (mean±SD) years (58% treated for hypertension) who were referred for ABPM during 1991 to 2005. Heart rate nondipping was defined as follows: (awake value−sleep value)/awake value. Linear and logistic regression models assessed covariate associations with ambulatory heart rate indices. All-cause mortality was analyzed by Cox proportional hazards modeling.

Results: Female sex, body mass index (calculated as weight in kilograms divided by height in meters squared), and treated diabetes were positively related to awake and sleep heart rate, whereas age and treated hypertension were inversely associated. All these variables were associated with lower sleep-related heart rate dipping magnitude. Multivariate-adjusted odds ratios (95% confidence intervals) for heart rate nondipping were 1.02 (1.02-1.03) per year of age; 1.05 (1.03-1.06) for body mass index; 1.39 (1.20-1.60) for women; 1.30 (1.12-1.51) for nappers; 2.19 (1.87-2.57) for treated hypertensive patients; and 1.38 (1.09-1.76) for treated diabetic patients. Mortality analysis according to deciles of the different heart rate variables showed a robust linear relationship only for heart rate dip and a hazard ratio of 2.67 (1.31-5.47) for the lowest vs the highest decile.

Conclusions: In clinical practice, ambulatory heart rate adds prognostic information beyond that of other ABPM predictors. Heart rate measures during sleep, and in particular the absence of dipping of heart rate to sleep levels, were independently associated with all-cause mortality.

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The prognostic importance of heart rate is inadequately recognized in clinical practice and in hypertension research. However, in recent years, evidence has been accumulating that heart rate is associated with cardiovascular and noncardiovascular death. Reviewing the relationship between heart rate and cardiovascular risk, Palatini and Julius concluded that an elevated heart rate, as well the unbalanced sympathetic outflow that it reflects, has pathophysiologic and prognostic implications beyond its association with increased blood pressure (BP) levels. The strength of the evidence, however, has been limited by inadequate standardization of heart rate measurement, in contrast to the office BP measurement technique, which is detailed extensively in guidelines and recommendations.

Ambulatory BP monitoring (ABPM) can potentially produce heart rate data under conditions of sleep and wakefulness over a 24-hour cycle. Heart rate is less dependent than BP on physical activity and is therefore less confounded by daily activities involving exercise or movement, which is a potential advantage for prediction of outcomes. Despite the accessibility to data generated during 24-hour ABPM, relatively few studies of ambulatory BP have also addressed ambulatory heart rate.

We studied data from a hospital-based ABPM service dataset, aiming to characterize the demographic, clinical, and prognostic (all-cause mortality) correlates of elevated ambulatory heart rate in this cohort. Our database is unique in that daytime sleep measurements are separated from awake measurements. We therefore focused on sleep heart rate and the sleep-related decrease in heart rate, which, to our knowledge, have been addressed in only 1 previous report.

METHODS

STUDY POPULATION

Data were extracted from our entire ABPM service database, from 1991 through 2005. All patients were included, except those younger than...
ABPM AND DEFINITIONS

Twenty-four-hour ABPM was undertaken with Spacelabs 90207 (Redmond, Washington), as previously described,10,31 conforming with current recommendations.2,35 Before 1999, we used Accutrack II (Suntech, Raleigh, North Carolina). The monitor was mounted on the nondominant arm between 8 and 10 AM and removed 24 hours later. Recordings were made every 20 minutes between 6 AM and midnight and every 30 minutes between midnight and 6 AM. A mercury sphygmomanometer was initially attached to the monitor through a Y-connector to verify agreement between the 2 modes of measurement (within a range of 5 mm Hg).

Cuff size was selected according to measured arm circumference: up to 24 cm, pediatric cuff; 24 to 32 cm, standard adult cuff; and over 32 cm, large adult cuff. The average of 2 to 3 initial sphygmomanometer measurements, taken by a trained technician after the subject had been seated for 5 minutes, was considered the patient’s clinic BP (normal, < 140 mm Hg systolic and < 90 mm Hg diastolic).11 The patients were instructed to record actual periods of sleep, including daytime naps (reported in 31%), in a diary. Sleep BP refers to the averages of all measurements taken during these periods. Patients were classified as having normal awake BP if the corresponding value was less than 135 mm Hg systolic and less than 85 mm Hg diastolic. The normal sleep BP was considered to be less than 120/70 mm Hg.2,13 The overall 24-hour normality was defined as less than 125/80 mm Hg.14 The normal dip was defined separately for systolic and diastolic BP as a 10% or greater reduction both for trend (df = 1) and for decile-specific hazards (df = 9!). Data are expressed as mean±SD or HR (95% confidence interval [CI]) unless otherwise specified. Two-sided nominal P < .05 was considered significant. Analyses were performed using SPSS version 13.0 (SPSS Inc, Chicago, Illinois).

STATISTICAL ANALYSES

Baseline characteristics were correlated with ambulatory heart rates by bivariate (demographics) or partial (ABPM measures) Pearson correlations. Multivariable general linear models with adjustment for age and sex were used to estimate mean heart rate (clinic, awake, sleep, and dip) according to baseline characteristics. Multivariate linear regression models evaluated predictors of ambulatory heart rates. In these models, significant interactions were noted for sex with other variables (age, BMI, BP, and treated hypertension) (supplementary tables, available from the authors). We explored the prediction of all-cause mortality by heart rate by comparing receiver operating characteristic curves. Hazard ratios (HRs) for death were computed by Cox proportional hazards models. Variables that were considered to be significant in univariate models were included in the multivariate analyses. Age was entered as an exponential term, exp(age), which was found to predict mortality more accurately than age. The assumption of proportional hazards, as assessed by introducing each predictor variable also as a time-dependent covariate, held in all Cox models. The relationship between ambulatory heart rate and mortality was initially evaluated by dividing the population according to heart rate deciles (the comparison of deciles was done by recoding the deciles with their median heart rate values and testing both for trend [df = 1] and for decile-specific hazards [df = 9!]).

RESULTS

PATIENTS’ CHARACTERISTICS AND DEMOGRAPHIC DATA

During the study period, 3957 patients (53% women), 58% of whom were treated for hypertension, underwent valid ABPM recordings in our service. Patient characteristics are presented in Table 1. There were 303 deaths during a mean follow-up of 7.0 years (range, 0.1-15.0 years), resulting in a mortality rate of 10.9 per 1000 patient-years.

HEART RATE AND DEMOGRAPHICS

Table 2 shows estimated heart rate means according to demographic variables (Pearson correlations between ambulatory heart rate and demographic variables can be found in the supplementary tables, which are available from the authors). Women had higher awake and sleep heart rates, as did patients with a higher BMI; age and treated hypertension were associated with lower heart rates, whereas treated diabetes was related to higher sleep heart rates. Female sex, BMI, age, treated hypertension, and treated diabetes were associated with reduced sleep-related heart rate dip. In a linear regression model predicting awake heart rate, there was a significant interaction between sex and treated hypertension (larger negative effect in women) (P < .001). With sleeping heart rate as

<table>
<thead>
<tr>
<th>Table 1. Clinical Characteristics of the Study Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>-------------</td>
</tr>
<tr>
<td>No. of patients</td>
</tr>
<tr>
<td>Age, mean±SD, y</td>
</tr>
<tr>
<td>BMI, mean±SD</td>
</tr>
<tr>
<td>Women, No. (%)</td>
</tr>
<tr>
<td>Treated diabetes, No. (%)</td>
</tr>
<tr>
<td>Treated hypertension, No. (%)</td>
</tr>
<tr>
<td>Nap, No. (%)</td>
</tr>
<tr>
<td>Follow-up, mean±SD, y</td>
</tr>
</tbody>
</table>

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).
Table 2. Estimated Mean Clinic and Ambulatory Heart Rate Indices Categorized According to Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Clinic</th>
<th>Awake</th>
<th>Sleep</th>
<th>Dip, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age below median</td>
<td>77.8±0.4</td>
<td>78.3±0.3</td>
<td>66.4±0.2</td>
<td>14.8±0.2</td>
</tr>
<tr>
<td>Age above median</td>
<td>69.5±0.3</td>
<td>69.1±0.3</td>
<td>61.5±0.2</td>
<td>10.5±0.2</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Men</td>
<td>72.4±0.4</td>
<td>72.2±0.3</td>
<td>61.9±0.2</td>
<td>13.5±0.2</td>
</tr>
<tr>
<td>Women</td>
<td>74.1±0.3</td>
<td>74.5±0.3</td>
<td>65.4±0.2</td>
<td>11.7±0.2</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No treatment</td>
<td>76.9±0.4</td>
<td>76.5±0.3</td>
<td>65.2±0.3</td>
<td>14.4±0.2</td>
</tr>
<tr>
<td>Treated hypertension</td>
<td>70.8±0.3</td>
<td>71.2±0.3</td>
<td>62.8±0.2</td>
<td>11.2±0.2</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No diabetes</td>
<td>73.3±0.3</td>
<td>73.3±0.2</td>
<td>63.6±0.2</td>
<td>12.7±0.2</td>
</tr>
<tr>
<td>Treated diabetes</td>
<td>74±0.8</td>
<td>74.3±0.6</td>
<td>66.1±0.5</td>
<td>10.3±0.5</td>
</tr>
<tr>
<td>P value</td>
<td>.42</td>
<td>.17</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI below median</td>
<td>73.4±0.3</td>
<td>73.2±0.3</td>
<td>62.9±0.2</td>
<td>13.4±0.2</td>
</tr>
<tr>
<td>BMI above median</td>
<td>73.3±0.3</td>
<td>73.6±0.3</td>
<td>64.7±0.2</td>
<td>11.6±0.2</td>
</tr>
<tr>
<td>P value</td>
<td>.71</td>
<td>.25</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No daytime nap</td>
<td>73.6±0.3</td>
<td>73.6±0.2</td>
<td>63.5±0.2</td>
<td>13.1±0.2</td>
</tr>
<tr>
<td>Daytime nap</td>
<td>72.8±0.3</td>
<td>72.3±0.3</td>
<td>64.5±0.3</td>
<td>11.3±0.3</td>
</tr>
<tr>
<td>P value</td>
<td>.11</td>
<td>.36</td>
<td>&lt;.01</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).
*Mean values were estimated using a multivariate general linear model.
The median age was 56.5 years, and the median BMI was 26.6. Values other than P values are expressed as mean±SEM.
*bModel adjusted for sex.
*cModel adjusted for age.
*dModel adjusted for sex and age.

the independent variable, age and treated hypertension interacted with sex (larger negative effects in women). Multivariate-adjusted odds ratios (95% CIs) for heart rate nondipping were 1.13 (1.10-1.16) per 5 years of age, 1.05 (1.03-1.06) per BMI unit, 1.39 (1.20-1.60) for women, 2.19 (1.87-2.57) for treated hypertensive patients, and 1.38 (1.09-1.76) for treated diabetic patients. Age was a more robust predictor of heart rate nondipping in men, while BMI was stronger among women (P<.01 for both interactions in linear regression models, supplementary tables).

THE EFFECT OF NAPPING

It has been previously shown that the decrease in heart rate during napping is lower than that during nighttime sleep.10 We therefore calculated the risk for heart rate nondipping among nappers compared with nonnappers and found a multivariate-adjusted odds ratio (95% CI) of 1.30 (1.12-1.51). However, in subsequent mortality analyses, inclusion of napping in Cox models did not significantly alter the HRs and was therefore omitted.

HEART RATE ASSOCIATIONS WITH OTHER AMBULATORY BP MEASURES

The various heart rate measures were significantly correlated with other ABPM-derived variables. Table 3 gives the partial correlation coefficients after age, sex, BMI, treated hypertension, treated diabetes, and napping were controlled for.

HEART RATE AND ALL-CAUSE MORTALITY

Heart rate dip, adjusted for covariates, predicted all-cause mortality slightly better than systolic BP dip, according to the area (±SEM) under the receiver operating characteristic curves (0.57±0.017 for heart rate dip vs 0.54±0.020 for systolic BP dip). Heart rate dip was superior to awake heart rate (0.513±0.018, P<.005) and sleeping heart rate (0.527±0.018, P=.05).

To evaluate the nature of the relationship between heart rate and mortality, we partitioned the population according to deciles of awake heart rate, sleep heart rate, and heart rate dip in Cox proportional hazards models that included demographic and treatment covariates. A plot of HRs for the heart rate deciles revealed the absence of a linear relationship between awake heart rate and all-cause mortality (P=.50 for trend, Figure 1A), while sleeping heart rate was moderately associated with mortality (P=.02 for trend, Figure 1B). Deciles of the heart rate dip, however, showed remarkably linear hazards (P<.001 for trend, Figure 1C). There was no significant interaction of sex with sleeping heart rate (P=.20) or with heart rate dip (P=.70). Compared with those with the highest dip (27±4 beats/min), patients in the lowest decile of heart rate dip (−3±7 beats/min) had an HR (95% CI) of 2.67 (1.31-5.47). Introducing systolic BP dip to the model did not materially affect the association (HR, 2.45 [95% CI, 1.19-5.03]).

We further examined heart rate dip as a continuous or dichotomous prognostic variable. After adjustment for covariates, the HR (95% CI) associated with decreased heart rate dip was 1.25 (1.13-1.39) per 1 SD. The HRs were similar when the systolic BP dip was included in the model (not shown). Categorically, heart rate nondipping (ie, <10% decrease in sleep) predicted all-cause mortality (adjusted HR, 1.45 [95% CI, 1.14-1.84]). With additional adjustment for systolic BP dipping status, the HR (95% CI) was 1.42 (1.11-1.80). We next evaluated the joint effect of both abnormal heart rate dipping and abnormal systolic BP dipping. In Cox proportional hazards modeling, which included demographic and treatment covariates, subjects with an abnormal heart rate dip (−3±7 beats/min) were more likely to have an abnormal systolic BP dip (95% CI) of 1.39 (0.98-1.98); subjects with an abnormal heart rate dip (but a normal systolic BP dip) had an HR (95% CI) of 1.46 (1.05-2.04); and subjects with both abnormal dips had an all-cause mortality HR (95% CI) of 1.90 (1.37-2.64) (Figure 2, overall P=.002).

ASSOCIATIONS AFTER EXCLUSION OF β-BLOCKER USE: A SUBSAMPLE ANALYSIS

β-Blockers might confound the association with heart rate variables. We were able to assess this issue in a subsample of patients with available data on specific drug treatment (n=1026). The subsample patients did not differ from the rest of the patients with regard to sex (P=.45), prevalence of treated hypertension (P=.37), clinic systolic BP (P=.22), 24-hour heart rate (P=.45), awake heart rate (P=.99), sleep heart rate (P=.79), or heart rate dip (P=.50). Patients with available data were somewhat older (mean±SD, 56.9±16.6 years vs 54.5±15.8 years), had
rate was stronger for systolic BP than for diastolic BP (with arguing against a confounding effect. In a summary of surveys in Western populations, Pala
ti and Julius1 found that the correlation for resting heart

dip compared with 0.97 (0.96-0.99) in the full sample, all-cause mortality was 0.91 (0.85-0.99) per 1% heart rate (n=677) were excluded. The adjusted HR (95% CI) for
rerun after the patients who were receiving 

determinants of the white coat effect and correlates of 

dip, % 0.038 c 0.073b −0.053b 0.192b
Sleep diastolic BP 0.154 b 0.206b 0.263b −0.073b
Sleep systolic BP 0.154 b 0.206b 0.263b −0.073b
Systolic BP dip, % 0.040b 0.066b −0.046b 0.165b
Diastolic BP dip, % 0.038b 0.073b −0.053b 0.192b

higher prevalence of diabetes (12% vs 7%), and a lower clinic diastolic BP value (83.1±12.6 mm Hg vs 86.1±12.4 mm Hg) than those without specific drug treatment information. The BMI differed slightly (27.5±4.6 vs 27.1±4.5, \(P=0.06\))

A Cox model that included age, sex, diabetes, BMI, and total number of antihypertensive medications was rerun after the patients who were receiving \(\beta\)-blockers (n=677) were excluded. The adjusted HR (95% CI) for all-cause mortality was 0.91 (0.85-0.99) per 1% heart rate dip compared with 0.97 (0.96-0.99) in the full sample, arguing against a confounding effect.

In a population of 3957 subjects referred for ABPM, the nocturnal heart rate reduction from awake levels, as well as heart rate during sleep, was associated with all-cause mortality. These findings were independent of potential confounding factors measured at baseline. The association of mortality with a nondipping heart rate pattern (<10%) was also independent of the BP dipping phenotype. In a subsample of patients who were not receiving \(\beta\)-blockers, heart rate dipping was still associated with lower mortality, indicating that the association that was demonstrated in the full sample is unlikely to be attributable to confounding by \(\beta\)-blocker use. These findings raise questions regarding the physiologic significance of ambulatory heart rate associations and the pathophysiologic implications of increased ambulatory heart rate, especially during sleep.

CORRELATIONS OF HEART RATE WITH AGE, BP, AND BMI

In a summary of surveys in Western populations, Palatini and Julius1 found that the correlation for resting heart rate was stronger for systolic BP than for diastolic BP (with possibly a stronger association in men). In our referred (predominantly hypertensive) population, correlations between clinic heart rate and clinic BP, as well as between ambulatory heart rate and ambulatory BP, were stronger for diastolic BP. However, the clinic heart rate may not adequately represent the basal heart rate.13 Indeed, previous investigations reported correlations between clinic heart rate and the “white coat effect,” but there was little correlation of heart rate with home or ambulatory BP.1,16 In our data set, however, clinic heart rate was similar to the awake measure and thus correlated well with both awake BP and clinic BP (although correlations with sleep BP were indeed smaller). This similarity may be attributable to the fact that age and sex (known determinants of the white coat effect and correlates of heart rate) were controlled for in our analyses.

Age was judged by Palatini and Julius1 to affect clinic heart rate only to a slight extent (−0.13 beats per year, adjusted), possibly more in women than in men.17 In our cohort, the adjusted ambulatory coefficients were in line with those previously reported for clinic heart rate, and indeed were larger in women. Therefore, in contrast to
BP, the clinic-awake heart rate difference did not increase with age (not shown). In our cohort, BMI and sex did not interact significantly for awake heart rate or for sleeping heart rate (supplementary tables).

HEART RATE DURING SLEEP

Heart rate during sleep is lower than during daytime.4,9,10,12,13 The magnitude of the difference, as well as its relation to other clinical variables, is not well characterized. As with BP, circadian heart rate changes are diminished or lost in conditions with sympathetic-parasympathetic imbalance, such as the persistent vegetative state.18 In our cohort, the median sleep-related heart rate dip was 12.7% (5th percentile, 1.5%; 95th percentile, 26.3%). Older individuals, women, subjects with a higher BMI, and patients treated for diabetes or hypertension had less dipping. Interestingly, age had a greater effect on men’s heart rate dip, while the BMI was stronger in women. Heart rate dipping correlated with both systolic and diastolic BP dipping even when common determinants were controlled for in the analysis.

AMBULATORY HEART RATE AND ALL-CAUSE MORTALITY

Heart rate was found to predict cardiovascular and all-cause death, in men more than in women,19 according to most studies. In our cohort, sleeping heart rate (positively) and the heart rate dip (inversely) predicted mortality regardless of sex. In fact, heart rate dipping during sleep was found to be a strong independent predictor of all-cause mortality. Adjustment for BP dipping (an established mortality predictor) did not weaken this association.

A 24-hour electrocardiography monitoring study was the first to report an association between average ambulatory heart rate and cardiovascular mortality.20 Subsequently, a small number of out-of-office BP outcome studies reported results pertaining to ambulatory heart rate. Verdecchia et al21 examined whether heart rate values that are recorded during 24-hour ABPM are independent predictors of survival in untreated essential hypertensive patients. Neither clinic nor 24-hour daytime or nighttime heart rates predicted total mortality. However, a blunted reduction of heart rate from day to night was associated with a multivariate adjusted HR (95% CI) of 1.30 (1.02-1.65) per 10% less reduction (compared with our 1.34 [1.10-1.48]). We are not aware of other previous studies that have examined the prognostic implications of blunted heart rate dipping. Palatini and colleagues2 reported that in elderly untreated hypertensive patients, ambulatory heart rate provided no additional information to the prediction of noncardiovascular mortality by conventional heart rate. A closer look, however, revealed that nighttime heart rate retained noncardiovascular predictive ability (HR, 1.74 [95% CI, 1.09-2.79] per 10 beats/min) in multivariate analysis that included conventional heart rate. In the Ohasama study, morning heart rate self-measured at home was predictive of cardiovascular mortality22 after home BP was accounted for.

PATHOPHYSIOLOGIC CONSIDERATIONS

In older subjects and in patients with preexisting disease, higher heart rate and mortality may be explained by low fitness, which is inversely associated with heart rate at all ages and in both sexes.23 A rapid heart rate may reflect loss of reserve in those with subclinical cardiovascular disease.

An alternative view on increased heart rate was provided by Schork et al,23 who identified (within the linear heart rate–BP relationship) a hyperkinetic subpopulation, characterized by higher heart rate, mean BP, cardiac output, and epinephrine levels. Linearity suggests that factors observed at the high end (hypertension) are also operative in the normotensive range, while bimodality indicates that hyperkinetic hypertensives are a separate subpopulation with a different underlying pathophysiologic state.1 Similarly, tachycardia in hypertension is caused by abnormal central nervous system autonomic output (enhanced sympathetic, decreased parasympathetic). Palatini and Julius1 suggested that underlying sympathetic overactivity in hypertension is conducive to atherosclerosis independently of BP elevation. An increased heart rate intensifies pulsatile flow, which may injure the endothelium,24 and deranged autonomic tone plays a critical role in potentially lethal cardiac arrhythmias.

The normal sympathetic withdrawal during sleep4,10,12,13,26 manifests itself in 24-hour ABPM by variation in both BP and heart rate. Heart rate is less dependent than BP on physical activity.4-7 Evidence of the integrity of the sympathetic nervous system is therefore demonstrated daily by dipping not only of BP but also of heart rate. We suggest that a sympathetic overactive state may be better represented by an elevated sleeping heart rate than by the clinic heart rate (owing in part to
poor standardization of the latter and the white coat effect) or by the awake heart rate (owing to its dependence on physical activity and fitness as well as sympathetic drive).

In conclusion, we found that heart rate data recorded routinely in an ABPM service add prognostic information beyond that of established ambulatory monitoring predictors. Heart rate measures during sleep, and in particular the absence of heart rate slowing, were independently associated with all-cause mortality. While further research is needed to better understand the associated pathophysiologic implications, clinicians may find prognostic value in these readily available measures.

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Author Contributions: All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Ben-Dov, Kark, and Bursztyn. Acquisition of data: Ben-Dov, Ben-Ishay, Mekler, Ben-Arie, and Bursztyn. Analysis and interpretation of data: Ben-Dov, Kark, and Bursztyn. Drafting of the manuscript: Ben-Dov and Bursztyn. Critical revision of the manuscript for important intellectual content: Kark, Ben-Ishay, and Bursztyn. Statistical analysis: Ben-Dov and Kark. Obtained funding: Bursztyn. Administrative, technical, and material support: Mekler and Bursztyn. Study supervision: Kark, Ben-Ishay, and Bursztyn.

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